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No. 07-

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

SUPPLEMENTAL APPENDIX

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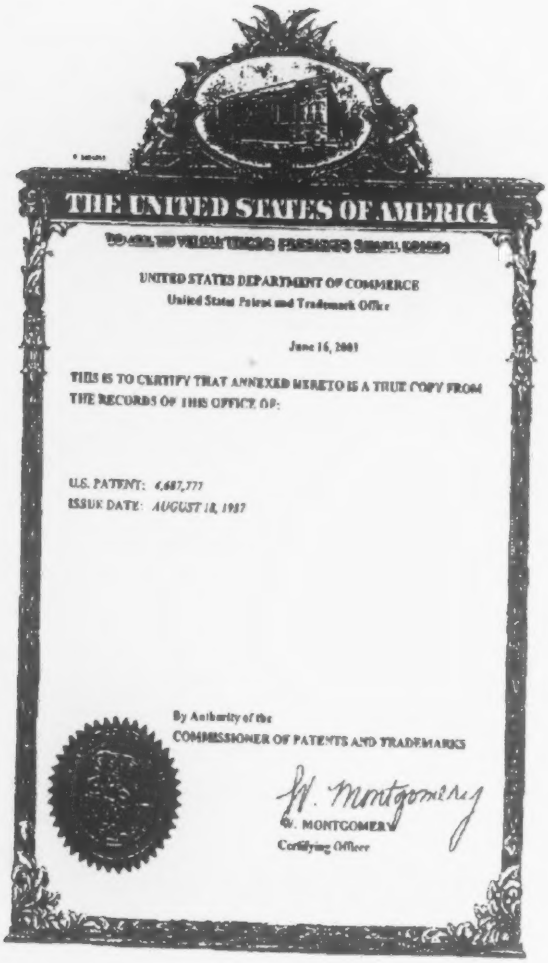
TABLE OF CONTENTS

	Page
U.S. Patent No. 4,687,777 (issued Aug. 18, 1987)	SA1
U.S. Patent No. 4,444,779 (issued Apr. 24, 1984)	SA8
Excerpts from File History of U.S. Patent No. 4,444,779	SA20
U.S. Patent No. 4,287,200 (issued Sept. 1, 1981)	SA28
Excerpts from File History of U.S. Patent No. 4,287,200	SA38
Studies on Antidiabetic Agents II ("Sohda II")	SA45
Excerpts from January 17, 2006 Transcript	SA66
Excerpts from January 24, 2006 Transcript	SA74
Excerpts from January 25, 2006 Transcript	SA86
1-1984 Monthly Report	SA90
Declaration of Henry I. Mosberg, Ph.D., dated Nov. 18, 2005	SA93
Declaration of Douglas R. Morton, Jr., Ph.D., dated Nov. 16, 2005	SA122

SA1



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THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *4,687,777*
ISSUE DATE: *AUGUST 18, 1987*

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M. Montgomery

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Certifying Officer

SA2

United States Patent [19]
Meguro et al.

[11] Patent Number: 4,687,777
[45] Date of Patent: Aug. 18, 1987

[54] THIAZOLIDINEDIONE DERIVATIVES, USEFUL AS ANTIDIABETIC AGENTS

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[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 820,390

[22] Filed: Jan. 17, 1986

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Jan. 19, 1985 [JP] Japan 60-8305

[51] Int. Cl.[4] A61K 31/44; C07D 417/04
[52] U.S. Cl. 514/343; 546/280
[58] Field of Search 546/280; 514/343

[56] References Cited

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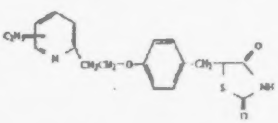
[57] ABSTRACT

Thiazolidinedione derivatives of the formula:



and pharmacologically acceptable salts thereof are novel compounds, which exhibit in mammals blood sugar- and lipid-lowering activity, and are of value as a therapeutic agent for treatment of diabetics and hyperlipemia.

5 Claims, No Drawings

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SA3

THIAZOLIDINEDIONE DERIVATIVES, USEFUL AS ANTIDIABETIC AGENTS

This invention relates to novel thiazolidinedione derivatives, a method of preparing them and antidiabetic agents containing same, which are utilized in the field of medicines.

A variety of biguanide and sulfonylurea derivatives have been used clinically as antidiabetic agents.

However, the biguanides are now scarcely used, because they tend to cause lactic acidosis, and use of the sulfonylureas, though they have strong hypoglycemic activities, requires sufficient precaution, because they frequently cause serious hypogly- cemia. Therefore, a new type of antidiabetic agent free from these defects has been desired.

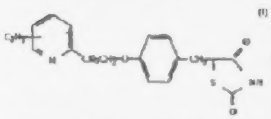
On the other hand, in Japanese Unexamined Patent Publication Nos. 224,36/1983 and 44586/1983, Chemical & Pharmaceutical Bulletin, 30, p. 3563 (1982), ibid. 30, p. 3580 (1982), and ibid. 32, p. 2267 (1984), reference is made to a variety of thiazolidinediones having blood glucose and lipid lowering actions. Antidiabetic activity of ciglitazone was also reported in Diabetes, 32, p. 804 (1983). These compounds, however, have not yet been put to practical use. As the reasons, (1) insufficient activities are found (2) serious toxicities may be mentioned.

The present inventors synthesized various compounds which are not concretely described in the above-mentioned publications of unexamined patent applications and have made studies on them to find the compounds exhibiting potent pharmacological effects with lower toxicity.

The present invention is to provide compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.

The present invention relates to:

1. A compound of the formula



(I)

or a pharmacologically acceptable salt thereof,

2. an antidiabetic agent, which contains as the effective component a compound of the formula (I) or a pharmacologically acceptable salt thereof, and

3. a method of preparing a compound of the formula (I) or a pharmacologically acceptable salt thereof, which comprises hydrolyzing a compound of the formula

The compounds representable by the above formula (I) include, specific cases,

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

The compound (I) of this invention contains both basic nitrogen and acid nitrogen in its molecule, and it can be converted to a pharmacologically acceptable salt, when desired, by using a suitable acid or base.

Such acid salts are exemplified by mineral salts (e.g. hydrochloride, hydrobromide, sulfate, etc.), organic acid salts (e.g. succinate, maleate, fumarate, oxalate, tartrate, etc.) and sulfonates (e.g. methanesulfonate, benzenesulfonate, toluenesulfonate, etc.). Such basic salts are exemplified by alkali metal salts e.g. sodium salt, potassium salt, alkaline earth metal salts, e.g. calcium salt, etc. All of these salts can be prepared by per se known means.

The compound (I) of this invention or a pharmacologically acceptable salt thereof exhibits blood-glucose and blood-lipid lowering action with lower toxicity, and may be safely administered, orally or parenterally, as it is or advantageously as a pharmaceutical composition comprising an effective amount of the compound (I) or its pharmacologically acceptable salt and a pharmacologically acceptable carrier, excipient or diluent therefor, in the form of for example, powder, granule, tablet, hard capsule, soft capsule, dry syrup, suppository, injection or the like.

The composition for oral administration such as powder, granule, tablet, hard capsule, soft capsule and dry syrup may be prepared by a per se known conventional manner, and may comprise carriers, excipients or diluents conventionally used in the pharmaceutical art. For example, suitable carriers or excipients include lactose, starch, sugar, magnesium stearate, etc. As the excipients in the preparation of soft capsules, there may be used nontoxic, pharmaceutically acceptable oils and fats of animal, vegetable or mineral origin. The essential active ingredients are generally dissolved in these oils and fats before filling soft capsules therewith.

The compositions for parenteral administration may, for example, be injections and suppositories. The injectable preparations may be prepared in the form of solutions or suspensions. Injectable preparations in the form of aqueous solutions may be prepared by a conventional manner. The suppositories for rectal administration can be prepared by incorporating the compound (I) or its pharmacologically acceptable salt with a conventional suppository base.

The pharmaceutical composition of the present application can be used as an antidiabetic agent for mammals including man.

Oral administration to an adult patient is 0.05-10 mg/kg body weight/day, preferably 0.3-5 mg/kg body weight/day, and parenterally 0.01-10 mg/kg body weight/day, preferably 0.1 1.0 mg/kg body weight/day once daily or divided into 2-4 times a week.

The compound represented by the above-mentioned general formula (I) and pharmacologically acceptable salts thereof [hereinafter collectively referred to as "Compound (I)"] can be prepared by subjecting a compound represented by the general formula (II) to hydro-

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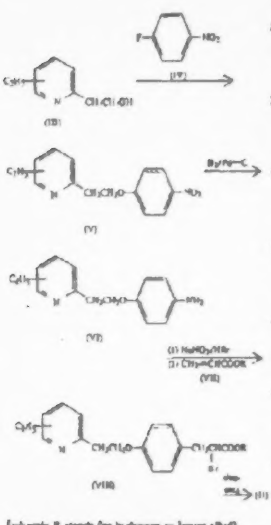
SA4

lysis. The reaction proceeds advantageously in a proper solvent by employing a mineral acid. The solvent is exemplified by alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, dioxane, tetrahydrofuran, dimethoxyethane, etc., and the mineral acid is exemplified by hydrochloric acid, hydrobromic acid, sulfuric acid, etc. The reaction temperature ranges from 30° C. to 150° C. The reaction time is 0.5–20 hours.

The compound (I) or a pharmacologically acceptable salt thereof produced as mentioned above can be collected and purified by conventional means such as concentration, extraction, recrystallization, chromatography, etc.

The compound represented by the above-mentioned general formula (II) can be produced by the following reactions.



[wherein R stands for hydrogen or lower alkyl].

The lower alkyl group represented by R is exemplified by (C_{1-4}) alkyl such as methyl, ethyl, propyl, isopropyl and butyl.

The reaction for producing compound (V) from compound (III) and compound (IV) is conducted in the presence of, for example, sodium hydride. This reaction can be carried out in a solvent e.g. dimethylformamide and tetrahydrofuran at a temperature ranging from −10° C. to 30° C. The reaction from compound (V) to compound (VI) can easily be conducted by conventional catalytic reduction employing, for example, palladium-carbon as the catalyst. Compound (VI) may be isolated as the pure product or can be subjected to the subsequent reaction step without isolation and purification. Compound (VIII) can be produced by subjecting compound (VI) to diazotization in the presence of an aqueous solution of hydrobromic acid, then allowing the resultant to react with acrylic acid or its lower alkyl ester (VII) in the presence of a copper catalyst e.g. cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, etc. (Meerwein arylation). Compound (VIII) can be purified by e.g. chromatography, and subjected to the subsequent reaction without isolation or purification.

Compound (VIII) is then allowed to react with thiourea to give compound (II). This reaction is carried out usually in alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, etc. The reaction temperature is usually 20°–180° C., preferably 60°–150° C. The amount of thiourea to be employed is 1–2 moles relative to one mole of compound (VIII).

In this reaction, as the reaction proceeds, hydrogen bromide is produced as the by product, and, for capturing this by-product, the reaction may be conducted in the presence of sodium acetate, potassium acetate, etc., in an amount of ca. by 1–4.5 mole relative to 1 mole of compound (VIII). The resultant compound (II) can be isolated, but may be subjected to the hydrolysis step directly without isolation.

(I) of the present invention has an excellent blood glucose and lipid lowering activity and is remarkably low in toxicity, which is supported by the following experimental data.

EXPERIMENTAL EXAMPLES

1. Blood Glucose and Lipid Lowering Activity in Mice

To male KK-A^y mice (8–10 weeks old, 5 mice/group), the test compounds (at three dosage levels) were given as a dietary admixture in CE-2 powdered diet (CLEA Japan) with free access to water for 4 days.

Blood samples were taken from the orbital vein on the 5th day.

Blood glucose and plasma triglyceride (TG) were determined by a glucose oxidase method and by using a commercially available assay kit, Clinotech TG-S (Iatron, Japan), respectively. Based on dose-response curves for blood glucose and plasma TG lowering activity, effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED25 (mg/kg/day) The results are shown in Table 1.

2. Lipid Lowering Activity in Rats

Male Sprague-Dawley rats (7 weeks old, 5 rats/group) were maintained on the laboratory chow (CE-2, CLEA, Japan) with free access to water. All the test compounds (at three dosage levels) suspended in 5% gum arabic solution were forcedly administered to the animals orally for 4 days. Blood samples were taken from the tail vein on the 5th day. Plasma TG was determined using a commercially available assay kit, Clinotech TG-S (Iatron). Based on dose-response curves for lipid lowering activity, effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED_{25} (mg/kg/day) The results are shown in Table 1.

3. Two-week Toxicity Study in Rats

Male and female Sprague-Dawley rats (5 weeks old, 5 rats/group) were maintained on the laboratory chow

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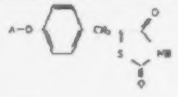
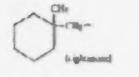
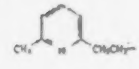
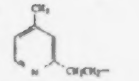
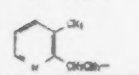
SA5

(CE-2, CLEA Japan) with free access to water. All the test compounds suspended in 5% gum arabic solution were forcedly administered orally to the animals for 2 weeks once daily. The dose was 100 mg/kg/day for every test compound. The animals were sacrificed in about 20 hours of fasting after termination of the two-week administration by withdrawing blood samples from the abdominal aorta using heparinized syringes under ether anesthesia. Liver and heart were removed and weighed. Hematology analysis was also carried out using an automatic cell counter. The data represent % increase or decrease from the control value (non-drug treated) as shown in Table I.

In Table I, Compound (I) of this invention is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with the compounds (a), (b), (d) and (e). Such an effect as above caused by the introduction of an ethyl group is quite unexpected. Thus, compound (I) of the present invention exhibits excellent hypoglycemic and hypolipidemic activities, and little toxicity to internal organs and blood even by continuous administration for a long period of time. Therefore, compound (I) is of value as a therapeutic agent for Type II diabetes accom-

TABLE I



Compound A	Blood Glucose ($P(O)_2$)	14(12-Dpl		Two-week toxicity (rat, p.o.)					
				Liver weight		Heart weight		number of erythrocyte	
	mg/dl	mg/dl	%	δ	♀	δ	♀	δ	♀
(I)	b	b	b	−0.7	−2.5	+0.9	−1.9	−5.4	−0.7
(a) 	40	41	70	+8.6*	+10.1*	+12.0*	+4.8	+3.3	−0.2
(b) 	4	3	5	+3.0	+10.2**	+15.9**	+11.8**	−2.9	8.1**
(c)	20	20	—	+1.3	−5.2	+3.1	+1.0	−4.1	−6.0
(d) 	20	19	—	+6.8*	+8.4**	+3.1	+1.7*	−6.3	−2.3
(e) 	18	19	—	−1.1	+6.6**	+10.9	+9.8*	−8.7*	−7.0**

note: *P < 0.05, **P < 0.01

In Table I, Compound (I) is a compound under the coverage of the present invention, compounds (a) and (b) are known compounds concretely referred to in the Japanese unexamined Patent Publication No. 22636/1980.

While compounds (c), (d) and (e) are not concretely referred to in the above-mentioned patent publication, as they are cited for comparison, since they are similar to compound (I) of this invention in basic chemical structures. As is apparent from the experimental results given

painted by obesity or hyperlipemia in mammals including rats.

EXAMPLE 1

(a) To a solution of 2 (5-ethyl-2-pyridyl)ethanol (33.0 g) and 4-fluorobenzotrifluoride (47.8 g) in DMF (300 ml) was added portionwise under ice-cooling 60% sodium hydride in oil (16.0 g). The mixture was stirred under ice-cooling for one hour, then at room temperature for 30 minutes, poured into water and extracted with ether.

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SA6

The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to give 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene as crystals (52.0 g, 62.9%). Recrystallization from ether-hexane gave colorless prisms, m.p. 53°-54° C.

(b) A solution of 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene (60.0 g) in methanol (500 ml) was hydrogenated at room temperature under one atmospheric pressure in the presence of 10% Pd-C (50% wet, 6.0 g). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in acetone (300 ml)-methanol (200 ml). To the solution was added a 47% HBr aqueous solution (152 g). The mixture was cooled, to which was added dropwise a solution of $NaNO_2$ (17.3 g) in water (30 ml) at a temperature not higher than 5° C. The whole mixture was stirred at 5° C. for 20 minutes, then methyl acrylate (112 g) was added thereto and the temperature was raised to 38° C. Cuprous oxide (2.0 g) was added to the mixture in small portions with vigorous stirring. The reaction mixture was stirred until nitrogen gas evolution ceased, and was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionate as a crude oil (76.09 g, 95.7%). IR(neat)cm^{-1}: 1735. NMR δ(ppm) in $CDCl_3$: 1.21 (3H, t, J=7), 2.80 (2H, q, J=7), 3.0–3.6 (4H, m), 3.66 (3H, s), 4.30 (2H, t, J=7), 4.3 (1H, m), 6.7–7.5 (6H, m), 8.35 (1H, d, J=2).

(c) A mixture of the crude oil of methyl 2-bromo-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionate (72.0 g) obtained in (b) thiourea (14.2 g), sodium acetate (15.1 g) and ethanol (300 ml) was stirred for 3 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the concentrate was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, to which were added water (200 ml) and ether (300 ml). The whole mixture was stirred for 10 minutes to yield 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone as crystals (60.7 g, 523.0%). Recrystallization from methanol gave colorless prisms, m.p. 187°–188° C. (decomp.). Elemental analysis for $C_{19}H_{21}N_3O_2S$ Calcd.: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.20; H, 5.84; N, 11.71.

(d) A solution of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone (23.5 g) in 3N HCl (200 ml) was refluxed for 6 hours. The solvent was evaporated off under reduced pressure, and the residue was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The crystals (23.5 g, 97.5%) which precipitated were collected by filtration and recrystallized from DMF-H_2O to give 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless needles (20.5 g, 86.9%), m.p. 183°–184° C.

Elemental Analysis for $C_{19}H_{20}N_2O_3S$ Calcd.: C, 64.02; H, 5.66; N, 7.86. Found: C, 63.70; H, 5.80; N, 8.01.

(e) To a suspension of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (356 mg) in methanol (10 ml) was added 28% sodium methylate/methanol solution (0.2 g) to make a solution. This solution was concentrated and diluted with ethyl ether to yield crystals. The crystals were collected by filtration and recrystallized from methanol-ethanol to give the sodium salt of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless crystals (298 mg, 73.8%), m.p. 262°–263° C. (decomp.).

Elemental analysis for $C_{19}H_{19}N_2O_3SNa$: Calcd.: C, 60.31; H, 5.06; N, 7.40. Found: C, 60.38; H, 5.02; N, 7.52.

EXAMPLE 3

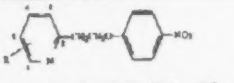
(1)	5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione	100 g
(2)	Lactose	70 g
(3)	Corn starch	15 g
(4)	Carboxymethyl cellulose calcium	94 g
(5)	Magnesium stearate	1 g
		280 g

The whole amounts of (1), (2) and (3) and 30 g of (4) were kneaded with water and dried in vacuo, followed by granulation. With the resultant granules were mixed 14 g of (4) and 1 g of (5) and the whole mixture was tableted with a tableting machine to give 1000 tablets 8 mm in diameter and each containing 100 mg of (1).

REFERENCE EXAMPLE 1

The compounds listed in Table 2 were prepared in accordance with Example 1-(a).

TABLE 2



R	mp	Recrystallization solvent	yield
3-CH_3	111–112° C.	ethyl acetate-hexane	62.9%
4-CH_3	75–76° C.	ethyl acetate-hexane	73.5%
5-CH_3	97–98° C.	ethyl acetate-hexane	72.3%

REFERENCE EXAMPLE 2

In accordance with Example 1-(b), the following compounds were prepared.

Methyl 2-bromo-3-[4-[2-(3-methyl-2-pyridyl)ethoxy]phenyl]propionate; IR(Nujol)cm^{-1}: 1735. NMR δ (ppm) in $CDCl_3$: 2.34 (3H, s), 3.10 (1H, dd, J=14 and 7), 3.25 (2H, t, J=6), 3.38 (1H, dd, J=14 and 7), 3.67 (3H, s), 4.29 (1H, t, J=7), 4.37 (2H, q, J=6), 6.8–7.5 (6H, m), 8.35 (1H, dd, J=5 and 2).

2-Bromo-3-[4-[2-(4-methyl-2-pyridyl)ethoxy]-phenyl]propionic acid methyl ester; IR(Nujol)cm^{-1}: 1735. NMR δ (ppm) in $CDCl_3$: 2.30 (3H, s), 3.10 (1H, dd, J=14 and 7), 3.36 (3H, t, J=7), 3.37 (1H, dd, J=14 and 7), 3.67 (3H, s), 4.30 (3H, t, J=7), 6.7–7.3(6H, m), 8.37 (1H, d, J=5).

REFERENCE EXAMPLE 3

A solution of 4-[2-(5-methyl-2-pyridyl)ethoxy]nitrobenzene (15.0 g) in methanol (150 ml) was subjected to catalytic reduction under 1 atmospheric pressure in the presence of 10% Pd-C (50% wet, 2.0 g). The catalyst was filtered off, and the filtrate was concentrated to give 4-[2-(5-methyl-2-pyridyl)ethoxy]aniline as crystals (12.3 g, 92.5%). Recrystallization from ethyl acetate-hexane gave colorless prisms, m.p. 74°–75° C.

Elemental analysis for $C_{14}H_{16}N_2O$: Calcd.: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.84; H, 7.17; N, 12.06.

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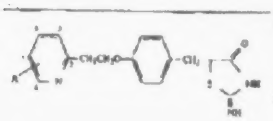
REFERENCE EXAMPLE 4

To a mixture of 4-[2-(5-methyl-2-pyridyl)ethoxy]benzaldehyde (12.8 g), 47% aqueous HBr solution (36.5 g) and methanol (40 ml)-acetone (80 ml) was added dropwise a solution of $NaNO_2$ (4.6 g) in water (10 ml) at 5° C. or below. The whole mixture was stirred at 5° C. for 20 minutes, then methyl acrylate (21.0 g) was added thereto and the temperature was raised to 38° C. Cuprous oxide (1.0 g) was added to the mixture in small portions with vigorous stirring. After nitrogen gas evolution had ceased, the reaction mixture was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-[4-[2-(5-methyl-2-pyridyl)ethoxy]phenyl]-propionate as a crude oil (17.3 g, 87.5%). IR(CH_2Cl_2)cm^{-1}: 1715. NMR δ (ppm) in $CDCl_3$: 2.27 (3H, s), 3.10 (1H, dd, J = 14 and 7), 3.72 (2H, t, J = 6), 3.80 (1H, dd, J = 14 and 7), 3.86 (3H, s), 4.29 (2H, t, J = 6), 4.32 (1H, t, J = 7), 6.7–7.5 (6H, m), 8.34 (1H, d, J = 2).

REFERENCE EXAMPLE 5

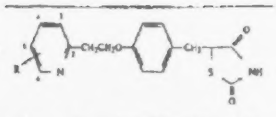
The compounds listed in Table 3 were prepared in accordance with Example 1-(a).



R	mp (decomp.)	Recrystallization solvent	yield
3-CH_3	116–118° C.	chloroform-methanol	75.1%
4-CH_3	150–161° C.	methanol	48.6%
5-CH_3	180–184° C.	chloroform-methanol	88.1%

REFERENCE EXAMPLE 6

The compounds listed in Table 4 were prepared in accordance with Example 1-(d).



R	mp	Recrystallization solvent	yield
3-CH_3	210–211° C.	DMF-water	85.7%
4-CH_3	178–179° C.	chloroform-methanol	72.4%

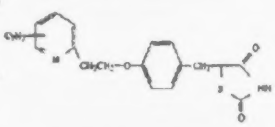
REFERENCE EXAMPLE 7

A mixture of 2-amino-5-[4-[2-(5-methyl-2-pyridyl)ethoxy]benzyl]-4-thiazolidinone (8.0 g), 2N HCl (90 ml) and ethanol (80 ml) was refluxed for 16 hours. The reaction solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate to yield crystals. The crystals were collected by filtration and recrystallized from ethanol to give 5-[4-[2-(5-methyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless prisms (7.0 g, 87.5%), m.p. 193°–193° C.

Elemental Analysis for $C_{21}H_{24}N_2O_3$: Calcd.: C, 63.36; H, 5.30; N, 8.10. Found: C, 63.22; H, 5.40; N, 8.11

We claim:

1. A compound of the formula:



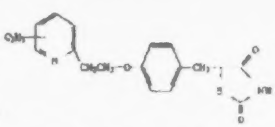
or a pharmacologically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

3. A compound as claimed in claim 1, wherein the compound is sodium salt of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

4. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

5. An antidiuretic composition which contains essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

* * * * *

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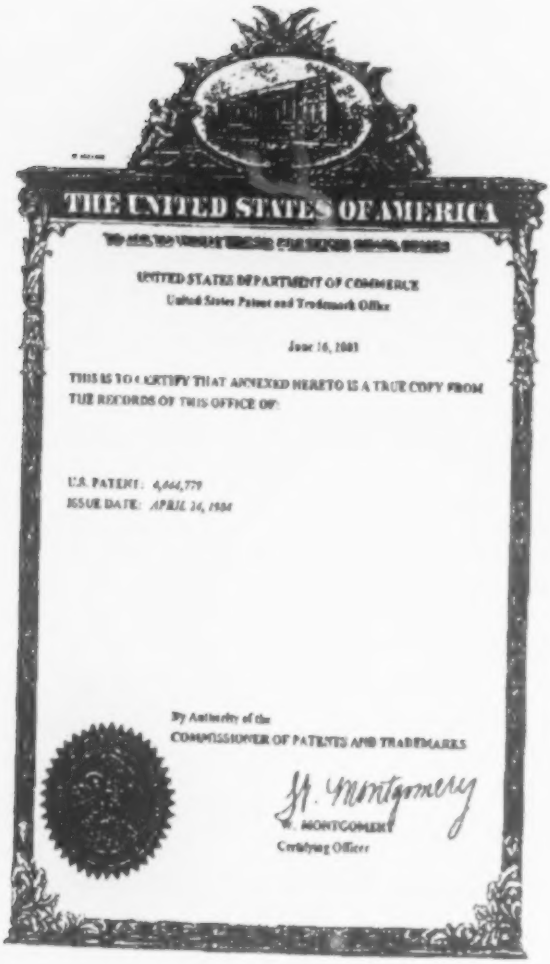

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U.S. PATENT: 4,644,779
ISSUE DATE: APRIL 26, 1984

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M. MONTGOMERY
Certifying Officer

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United States Patent [19]
Kawamatsu et al.

[11] 4,444,779
[45] * Apr. 24, 1984

[54] THIAZOLIDINE DERIVATIVES

[75] Inventors: Yutaka Kawamatsu, Kyoto; Takaaki Fujita, Takarazuka, both of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[*] Notice: The portion of the term of this patent subsequent to Jul. 20, 1999 has been disclaimed.

[21] Appl. No.: 478,013

[22] Filed: Mar. 15, 1983

Related U.S. Application Data

[62] Division of Ser. No. 295,093, Feb. 7, 1981, which is a division of Ser. No. 258,536, Apr. 29, 1981, Pat. No. 4,340,608, which is a division of Ser. No. 62,542, Jul. 27, 1979, Pat. No. 4,287,200.

[30] Foreign Application Priority Data

Aug. 4, 1978 [JP] Japan 53-95871

[51] Int. Cl.³ C07D 277/20; A61K 31/425
[52] U.S. Cl. 424/263; 424/270; 546/194; 548/208; 548/202; 548/203
[58] Field of Search 548/202, 203, 204; 424/263, 270; 546/208, 334

[56] References Cited

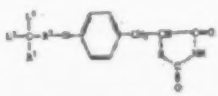
U.S. PATENT DOCUMENTS

4,340,608 7/1982 Kawamatsu et al. 424/263

Primary Examiner—Nicholas S. Rizzo
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

Thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group having one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur or a group of the formula

(where R^2 and R^3 are the same or different and each is lower alkyl or R^2 and R^3 are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring), R^0 means a bond or a lower alkylene group, L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen, respectively] are novel compounds and useful as, for example, remedies for diabetes, hypolipidemia and so on of mammals including human beings.

8 Claims, No Drawings

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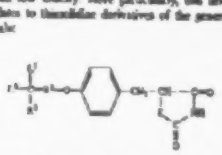
THIAZOLIDINE DERIVATIVES

This is a division of application Ser. No. 396,080 filed July 7, 1982, which is a division of application Ser. No. 258,554, filed Apr. 29, 1981, now U.S. Pat. No. 4,340,605, which in turn is a division of application Ser. No. 62,512 filed July 27, 1979, now U.S. Pat. No. 4,287,200.

This invention relates to novel thiazolidine derivatives having hypoglycemic and hypoglycemic activities with low toxicity. More particularly, this invention relates to thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur, or a group of the formula

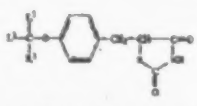
(where R^3 and R^4 are the same or different and each means lower alkyl or R^3 and R^4 are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring as taken together with the nitrogen atom adjacent to R^3 and R^4); L^1 is a bond or a lower alkylene group; L^2 and L^3 may be the same or different and each is lower alkyl or L^1 and L^2 are combined to each other to form an alkylene group, provided that when R^1 is other than alkyl, L^2 and L^3 may further be hydrogen, respectively].

Referring to the general formula (I), the alkyl group R^1 may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; the cycloalkyl group R^1 may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R^1 may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R^1 may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R^1 is

the lower alkyls R^3 and R^4 may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and n-butyl. When R^3 and R^4 are combined to each other to form a 5- or 6-membered heterocyclic

group as taken together with the adjacent N atom, i.e. in the form of

the heterocyclic group may further include a hetero-atom selected from among nitrogen, oxygen and sulfur, as exemplified by piperidino, morpholino, pyrrolidino and piperazino. The lower alkylene group R^2 may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene. The bond R^2 is equivalent to the symbol "—" or the like which is used in chemical structural formulas, and when R^2 represents such a bond, the compound of general formula (I) is represented by the following general formula (II):



(II)

Thus, when R^2 is a bond, the atom adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L^2 and L^3, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L^2 and L^3 are joined together is a group of the formula —$(CH_2)_n$— [wherein n is an integer of 2 to 6.] The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, as well as said heterocyclic group

may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.), lower alkoxy groups (e.g. methoxy, ethoxy, etc.), halogens (e.g. chlorine, bromine, etc.) and hydroxyl. The case also falls within the scope of the general formula [I] that an alkylenedioxy group of the formula —O—$(CH_2)_m$—O— [m is an integer of 1 or 2], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The compound (I) according to this invention can be converted to various salts by procedures known per se. For example, when the heterocyclic group R^1 includes a tertiary nitrogen atom, or R^1 means a group of the formula

the compound (I) can be converted to acid salts with acids, such as hydrochloric acid, sulfuric acid, acetic acid, oxalic acid, etc. When R^1 does not include a tertiary nitrogen atom, the compound may be converted to salts with cations such as a sodium ion, a potassium ion, a calcium ion, or an ammonium ion, etc.

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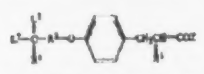
The thiazolidine derivative (I) according to this invention has activity to lower the blood sugar and triglyceride levels in mice (KKAy) with spontaneous diabetes and is expected to be of value in the treatment of hyperlipemia, diabetes and their complications in mammals including human beings. The compound (I) has low toxicity. For example, the LD$_{50}$ value of 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione in a rat is more than 10 g/kg. (P.O.). The compound (I) may be orally administered in such dosage forms as tablets, capsules, powders, granules, etc. or by other routes in such forms as injections, suppositories, pellets and so on. Taking the treatment of hyperlipemia as an example, the compound may be orally or otherwise administered at a normal daily dose level of 50 mg to 1 gram per adult human. For the treatment of diabetes, the compound (I) may be orally or otherwise administered at a normal daily dose of 10 mg to 1 gram per adult human.

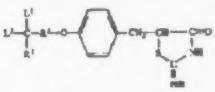
The thiazolidine derivative (I) of this invention may be produced, for example, by the following methods.

(1) The thiazolidine derivative (I) can be produced by the steps of reacting a compound of general formula (III) with thiourea to obtain an 2-iminothiazolidin-4-one derivative of general the formula (IV) and, then, hydrolyzing the last mentioned derivative (IV).



(III)

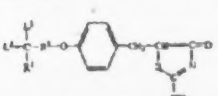
[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore; X^1 means halogen (e.g. chlorine, bromine, etc.), alkylsulfonyloxy (e.g. methylsulfonyloxy, etc.) or arylsulfonyloxy (e.g. toluenesulfonyloxy, etc.); Y is lower alkoxy (e.g. methoxy, ethoxy, etc.), hydroxyl, amino or a group of the formula —OM (M is, for example, an alkali metal) or, e.g. Na, K, etc., or NH$_4$]



(IV)

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore]

The compound (IV) may tautomerically take the form as below:

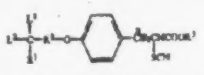


(IV')

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore] The compound (IV') is also included within the scope of this invention. In this specification, the nomenclature and formula of these compounds are described on this as "2-iminothiazolidine derivatives" and as formula (IV), respectively.

The reaction between a compound (III) and thiourea is normally conducted in a solvent. As examples of such solvent may be mentioned alcohols (e.g. methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.), acetone, dimethylsulfoxide, sulfolane, dimethylformamide, etc. While the relative amounts of starting materials need not be critically controlled, it is normally desirable to employ a slight excess of thiourea based on compound (III). Then, 1 to 2 molecular equivalents of thiourea is preferably employed relative to compound (III). While the conditions of reaction such as reaction temperature and time depend on such factors as the starting material, solvent, etc., this reaction is normally carried out at the boiling point of the solvent used or at 100° to 130° C. for a few to ten and odd hours. The sparingly soluble imino-compound (IV) is produced as the above manner. This imino-compound (IV) may be isolated prior to the following hydrolysis step or the reaction mixture containing (IV) may be directly hydrolyzed. In the hydrolysis step, the imino-compound (IV) is heated in a suitable solvent (e.g. mildsolvent) and in the presence of water and mineral acid. The acid just mentioned is added normally in a proportion of 0.1 to 10 molecular equivalents, preferably 0.2 to 3 equivalents, based on compound (III), while water is used normally in large excess based on compound (III). The heating time normally ranges from a few hours to 10 and odd hours.

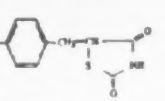
(2) The thiazolidine derivative (I) can further be produced by subjecting a compound of formula:



(V)

[wherein L^1, L^2, R^1 and R^2 have the meanings given above, and R^3 means alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, n-propyl, n-butyl, t-butyl, etc.), aryl having 6 to 8 carbon atoms (e.g. tolyl, etc.) or aralkyl having 7 to 8 carbon atoms (e.g. benzyl, etc.)] to a cyclization reaction. This cyclization reaction is usually carried out by hydrolyzing a compound (V) with water. The hydrolysis is generally conducted in the presence of a catalyst, examples of which include hydrogen halides (e.g. hydrogen chloride, hydrogen bromide), mineral acids such as hydrochloric acid, sulfuric acid, etc. The catalyst may generally be used in an amount of 20 to 50 mol equivalents relative to the compound (V). This reaction may be conducted in the presence of an organic solvent such as alcohol (e.g. methanol, ethanol, etc.). While the reaction temperature varies with the type of catalyst used, the reaction may generally be carried out at a temperature ranging 50° to 150° C. The reaction time is usually in the range of 2 to 30 hours.

(3) The thiazolidine derivative (I) can also be produced by reacting compound of the formula:



(VI)

with a compound of the formula:

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(VII)

(wherein L^1, L^2, R^1 and R^2 have the meanings given above, and X^2 means a halogen atom such as chlorine, bromine, etc.) in the presence of a base. As the base, there may be mentioned sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. This reaction is usually carried out in the presence of a solvent. As a suitable solvent, there may be mentioned dimethylformamide, dimethylsulfoxide, etc. The reaction temperature may be in the range of room temperature to 80° C.

The resulting thiazolidine derivative (I) can be isolated and purified by conventional procedures such as concentration at atmospheric or subatmospheric pressure, solvent extraction, crystallization, recrystallization, plastic transfer, chromatography, etc.

The compound (III) which is used as the starting material in the above preparation method (I) can be produced, for example, by the steps of dissolving the corresponding sulfide compound and subjecting the thiazo-compound to bromoxin oxydation.

The following reference and working examples are given to illustrate this invention in further detail.

REFERENCE EXAMPLE 1

In 200 ml of methanol is dissolved 19.0 g of 4-[2-(N,N-dimethylaminoethylthio)-benzoyl]benzonitrile and after 3 g of 10% Pd-C (50% wet) is added, catalytic reduction is carried out at atmospheric temperature and pressure. The reaction system absorbs about 4.4 l of hydrogen in 75 minutes. The catalyst is then filtered off, the filtrate is concentrated under reduced pressure and the oily residue is dissolved in a mixture of 300 ml methanol and 100 ml acetone. Following the addition of 21.3 ml of concentrated hydrochloric acid, the solution is cooled to 0° C. and a solution of 4.9 g sodium nitrite in 10 ml water is added dropwise at a temperature not exceeding 5° C. The mixture is stirred at 5° C. for 30 minutes, at the end of which time 33.3 g (34.9 ml) of methyl acrylate is added. The reaction mixture is heated to 35° C. and 1 g of cuprous oxide is added in small portions, whereupon the temperature of the reaction system rises to 44° C. with the evolution of nitrogen gas. The mixture is stirred for one hour and after the temperature has dropped to room temperature, it is allowed to stand overnight. The solvent is then distilled off under reduced pressure and the residue is made strongly basic with concentrated aqueous ammonia. Then, following the addition of water, extraction is carried out with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate. The oily residue is chromatographed on a column of 200 g silica gel, elution being carried out with ether-n-hexane (1:4). By the above procedure is obtained 10.7 g (44.8%) of methyl 3-chloro-3-[4-[2-(N,N-dimethylamino)-ethylthio]-benzoyl]-propionate.

IR (liquid film) $\nu_{max}^{cm^{-1}}$: 2945, 2820, 1745, 1675, 1595, 1250, 1170, 1020

NMR δppm $CDCl_3$: 0.93(6H, t), 1.2–1.36(6H, m), 2.52(4H, t), 2.82(2H, t), 3.0–3.92(2H, m), 3.92(3H, s), 4.0(2H, t), 4.4(1H, t), 6.75–7.38(4H, q)

EXAMPLE 1

(a) A mixture of 3.6 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate, 0.73 g of thiourea and 3 ml of sulfolane is heated at 120° C. for 4 hours and after cooling, 15 ml of water is added. The oil is separated, ether is added to the oil and the crystalline insolubles (a) are separated from the solution (b) by filtration. The filtrate (b) is distilled to remove the solvent and the residue is run onto a column of 100 g silica gel, elution being carried out with chloroform. By the above procedure is obtained 1.7 g of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione. m.p. 107°–108° C. (benzene-ligroin)

On the other hand, crystals (a) are recrystallized from ethanol-acetone (3:1) to obtain 1 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidin-4-one with a decomposition point of 210°–212° C. A 300 mg portion of this crystalline product is boiled with 2 ml of sulfolane and 2 ml of 6 N-HCl at 110° C. for 5 hours. After cooling, 50 ml of water is added and the resulting crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 250 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

EXAMPLE 2

A mixture of 27 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate, 11 g of thiourea and 60 ml of sulfolane is heated at 110° C. for 6 hours and, then, boiled with 30 ml of 2 N-sulfuric acid (or 2 ml of 6 N-HCl) for 16 hours. After cooling, 1 l of water is added and the oil is separated and allowed to stand for a while, whereupon crystals separate out. These crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 15.9 g of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

EXAMPLE 3

(a) 393 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionic acid and 150 mg of thiourea are heated with 2 ml of sulfolane at 120° C. for 1.5 hours and, following the addition of 2 ml of 6 N-HCl, the mixture is further heated for 3 hours, at the end of which time 10 ml of water is added. The resulting crystals are recovered by filtration. By the above procedure is obtained 310 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(b) The same procedure as that described in (a) is repeated except that 355 mg of sodium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate is employed. By this procedure is obtained 330 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(c) The same procedure as that described in (a) is repeated except that 332 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionamide is employed. By this procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(d) In 10 ml of ethanol are dissolved 1.0 g of ω-bromo-2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate and 0.8 g of thiourea and the solution is heated for 3 hours, at the end of which time 50 ml of water is added.

By the above procedure is obtained 1.0 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidin-4-one.

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EXAMPLE 4

In 2 ml of dimethylsulfoxide are dissolved 208 mg of 3-bromo-3-[4-(4-chlorobenzyloxy)phenyl]propionic acid and 100 mg of thiourea, and the solution is heated at 140° C. for 3 hours. Then, after 0.5 ml of water is added, the solution is further heated for 5 hours. Then, 10 ml of water is added and the resulting crystals are recovered by filtration and recrystallized from benzene-n-hexane (1:1). By the above procedure is obtained 170 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 5

1.9 g of ethyl 3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-2-thiocyanatopropionate is dissolved in 20 ml of ethanol and to the solution 20 ml of 6 N-hydrochloric acid is added. The mixture is refluxed for 24 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ether. The extract is washed with water and then dried. After distilling off ether, the residue is crystallized from ether-n-hexane, whereby 710 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]thiazolidine-2,4-dione is obtained.

EXAMPLE 6

2.1 g of ethyl 2-methanesulfonyloxy-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate and 0.76 g of thiourea are added to 20 ml of sulfolane, and the mixture is heated at 120° C. with stirring for one hour. After adding 10 ml of 2 N-hydrochloric acid, the mixture is heated at 100° C. for 8 hours. After cooling, water is added to the mixture, and the mixture is subjected to extraction with ether. The extract is washed with water and dried. The ether is distilled off to give 1.3 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 7

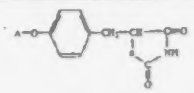
2.0 g of ethyl 2-methanesulfonyloxy-3-[4-(1-methyl-cyclohexylmethyloxy)phenyl]propionate and 760 mg. of thiourea are added to 20 ml of ethanol. The mixture is refluxed for 2 hours. To the mixture is added 10 ml of hydrochloric acid, and the mixture is further refluxed for 16 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ethyl acetate. The extract is washed with water and dried. The ethyl acetate is distilled off to give 1.4 g of 5-[4-(1-methyl-cyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione. Crystallization from 95% ethanol gives crystals melting at 150°–151° C.

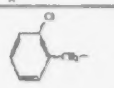
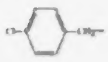
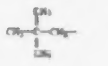
EXAMPLE 8

To 12 ml of dimethylsulfoxide is dissolved 1.12 g of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione, and 400 mg of 50% sodium hydride in oil is added to the solution. The mixture is stirred at room temperature for 15 minutes, to which is added 0.81 g of 4-chlorobenzyl chloride. The whole mixture is stirred at 50° C. for 4 hours. Water is added to the mixture and the mixture is acidified with 2 N-hydrochloric acid. The mixture is subjected to extraction with ether. The extract is washed with water and dried. Ether is distilled off to give an oily substance. The oily substance is subjected to column chromatography on 30 g silica gel, elution being carried out with cyclohexane-ethyl acetate (2:1). By the above procedure there was obtained 425 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 9

By procedures analogous to those described above in Examples 1 to 4, the following compounds were synthesized.



Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1		Benzene-n-hexane	89–94	1,5
2		Benzene-cyclohexane	125–126	1
3		Benzene-Ligroin	126–128	1,3
4		Isopropyl ether	128–129	1

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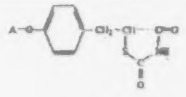
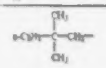
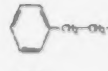
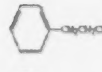
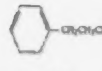
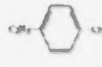


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
5		Ether-n-hexane	98–104	1,2
6		Cyclohexane	108–110	1
7		Cyclohexane	106–108	2
8		Cyclohexane	101–103	1
9		Cyclohexane	101–102	2
10		Ether-n-hexane	101–103	1,2
11		n-Hexane	68–70	3
12		Benzene-ligroin	93–95	1,2
13		Ethyl acetate-cyclohexane	95–98	1
14		Ethyl acetate-cyclohexane	82–83	1
15		Ethyl acetate-n-hexane	110–114	3
16		Ether-n-hexane	93–95	3

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SA15

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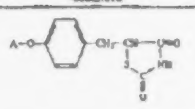
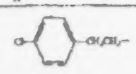
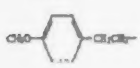
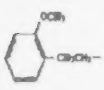
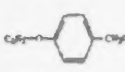
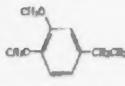
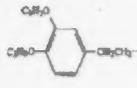
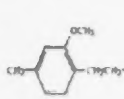
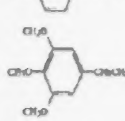
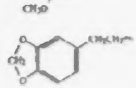
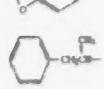


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No(s).
17		Ethyl acetate	143–145	2
18		Ethyl acetate + hexane	144–146	2
19		Ethanol-hexane	72–73	2
20		Ethyl acetate-n-hexane	68–70	2
21		Ethanol-hexane	110–111	2
22		Oil (Diffuse reflection) 2900, 1730, 1700, 1600, 1460 cm^{-1}		3
23		Ethyl acetate-n-hexane	92–93	1
24		Ethyl acetate-n-hexane	104.5–105.5	2
25		Ethyl acetate-ether	131–133	2
26		Ethanol-hexane	84–85	1

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SA16

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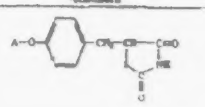
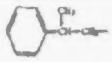
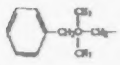
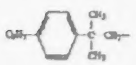
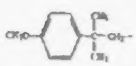
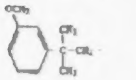
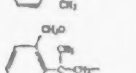
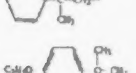
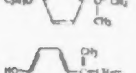
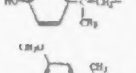


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No(s).
27		Ethanol-hexane	66-67	13
28		Ethanol-hexane	107-108	1
29		Cyclohexane	106-107	2
30		Ethanol-hexane	104-105	2
31		Ethanol-hexane	107-108	2
32		Ethanol-hexane	66-67	2
33		Ethanol-hexane	110-111	2
34		Ethanol-hexane	65-66	2
35		Ether	171-172	2
36		Ethanol-hexane	104-105	1
37		Methanol	140-156	1

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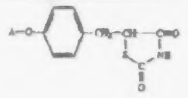
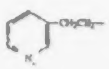
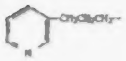
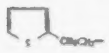
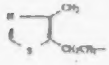
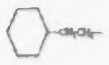


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example Method
38		Chloroform-methanol	175–176	12
39		Chloroform-methanol	176–177	1
40		DMF—H$_2$O	209–210	12
41		Methanol	167–168	1
42		Ethyl acetate-n-hexane	103–104	1
43		Ethanol-water	73–74	1
44		Ethanol-water	63–64	1
45		Ethanol	183–184.5	1
46		Cyclohexane	82–83	1
47		n-Propanol	131–132	12
48		Benzene-hexane	154–155	12

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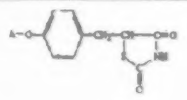
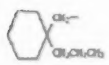


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
47		Cyclohexane	124-125	1,5
49		Ligroin	88-89	1
51		n-Hexane	68-69	1
52		Benzene-ligroin	136-137	1
53		Ether-n-hexane	88-89	1
54		Ether-n-hexane	110-111	1

EXAMPLE 10

A mixture of 10.0 g methyl 2-chloro-2-[4-(2-morpholinoethyl)oxyphenyl]propionate and 6.44 g thiourea is heated in the presence of 100 ml of sulfolane at 120° C. for 4 hours. After cooling, a saturated aqueous solution of sodium hydrogen carbonate is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 4.1 g (40.2%) of 2-imino-5-[4-(2-morpholinoethyl)oxyphenylthiazolidin-4-one is obtained as crystals. These crystals are recrystallized from ethyl acetate-methanol. Colorless needles, m.p. 159°-160° C.

In 20 ml of 2 N-HCl is dissolved 4.1 g of the above 2-imino-5-[4-(2-morpholinoethyl)oxybenzyl]thiazolidin-4-one and the solution is heated under reflux for 16 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 3.5 g (90.7%) of 5-[4-(2-morpholinoethyl)oxybenzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from dimethylformamide-water. Colorless prisms, m.p. 188°-189° C.

EXAMPLE 11

A mixture of 9.0 g methyl 2-chloro-2-[4-(N,N-dimethoxyethoxyethyl)oxyphenyl]propionate and 2.4 g thiourea is heated in the presence of 100 ml of n-butanol at 100° C. for 15 hours. After cooling, the n-butanol is distilled off under reduced pressure, 100 ml of 2 N-HCl is added to the residue and the mixture is heated at 100° C. for 4 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried (over Na_2SO_4) and distilled to remove the ethyl acetate, whereupon 6.0 g (83.1%) of 5-[4-(2,N-dihydroxypropylamino)ethyloxybenzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from ethanol. Colorless prisms, m.p. 134° -135° C.

EXAMPLE 12

By procedures analogous to those described in Example 10 or 11, the following compounds were synthesized

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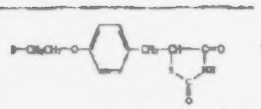


Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1	.HCl	Ethanol	280–289	10, 11
2	.HCl	Ethanol	245–247	10, 11
3		Ethanol	120–122	11
4		Ethanol	130–135	11
5		Ethanol	98–99	10, 11
6	.HCl	Methanol	222–224	11
7	.HCl	Methanol	244–245	11

EXAMPLE 19

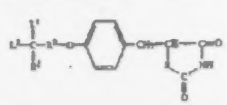
An example of practical recipe in which the compound of this invention is utilized as remedies for diabetes is as follows

(Tablets)		
(1)	5-[4-(2-methyl-5-benzoyloxybenzoyloxy)benzyl]thiazolidine-2,4-dione	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	microcrystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
		230 mg per tablet

(1), (2), (3) and ½ quantity of (4) are thoroughly mixed, and then the mixture is granulated. Remaining ½ quantity of (4), and (5) are added to the granules and compressed into tablets. Thus prepared tablets can further be coated with a suitable coating agent.

What is claimed is:

1. A thiazolidine derivative of the formula:



wherein R^1 is a pyridyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, m is thienyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, R^3 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is hydrogen, lower alkyl or L^1 and L^2 are combined to form an alkylene group.

2. A thiazolidine derivative as claimed in claim 1, each of L^1 and L^2 is hydrogen.

3. A thiazolidine derivative as claimed in claim 2, wherein R^3 is a lower alkylene group having 1 to 3 carbon atoms.

4. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione.

5. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(4-methyl-5-thienyl)ethoxy]benzyl]thiazolidine-2,4-dione.

6. A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in claim 1 and a pharmaceutically acceptable carrier therefor.

* * * * *

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241-97-198
S3
4-62-47-3-1

REGULAR UTILITY

Form PTO-436
(Rev. 8/78)

4444779

SERIAL NUMBER (series of 1979)	PATENT DATE	PATENT NUMBER
476017	APR 24 1984	[redacted]

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
476,017	03/15/83 RULE 60	568		122	

APPLICANT: YUTAKA KAWAMATSU, KYOTO, JAPAN; TOKUSHI FUJITA, TAKARAZUKA, JAPAN.

CONTINUING DATA********
VERIFIED THIS APPLN IS A DIV OF 06/596,723 [illegible]
WHICH IS A DIV OF 06/259,554 [illegible] PAT 4,340,605
WHICH IS A DIV OF 06/062,512 [illegible] PAT 4,287,200

FOREIGN/PCT APPLICATIONS********
VERIFIED JAPAN 55-[illegible]/1978 [illegible]

H12

Foreign priority claimed: yes / no — 35 USC 119 conditions met: yes / no — Verified and Acknowledged: Examiner's Initials

AS FILED

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
JPY	3	6	1	$ 336.00	

WENDEROTH, LIND AND PONACK
~~SUITE 4106~~ Suite 700
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WASHINGTON, DC 20006

TITLE: [illegible]

U.S. DEPT. of COMM.-Pat. & TM Office — PTO-436L (Rev. 10-78)

241-97-198
83
4-62-47-3-1

PARTS OF APPLICATION FILED SEPARATELY

PREPARED FOR ISSUE

(Assistant Examiner) (Issue Clerk)

AT ALLOWANCE

SHEETS DRAWING	FIGURES DRAWING	CLAIMS	CLASS	SUBCLASS
4	16	16	424	263

EXAMINED AND PASSED FOR ISSUE

NICHOLAS S. RIZZO
PRIMARY EXAMINER
(Primary Examiner) (Art Unit)

(Claim for printing figure) | (Number of printed claims) | Issue fee due (ISL)

Division | Series | $500.

Notice of Allowance and issue fee due (ISL)

Date mailed: 11/24/83 | Date paid:

Form PTO-436-O.G. DEPT. OF COMMERCE (Rev. 6-78) PAT. & TM OFF

DISCLAIMER LABEL

SERIAL NO.	FILING DATE
476,017	3-15-83

A terminal disclaimer has been entered and recorded under 35 U.S.C. 253 to date this by Patent Issue Division.

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476017

3/18/83 BW 5/3/83

MAR 15 1983

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
YUTAKA KAWAMATSU ET AL. :
Filed March 15, 1983 : Group Art Unit 122
THIAZOLIDINE DERIVATIVES : Examiner N. Rizzo
[This is a Divisional of :
Serial No. 396,093 :
Filed July 7, 1982] :

PRELIMINARY AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C.

Sir:

Kindly amend the above-identified application as follows:

In the Specification:

Page 4, line 11, after "as" insert -- a -- and change "potassiumion" to -- a potassium ion --;

line 12, change "calciumion, ammoniumion" to -- a calcium ion, or an ammonium ion --;

line 19, after "example" insert -- , the -- and change "valule" to -- value --;

line 21, after "in" insert -- a --.

Page 5, line 9, after "general" insert -- the --.

Page 7, line 12, after "to" insert -- a --;

line 19, change "equivalent" to -- equivalents --;

line 21, after "of" insert -- an --.

Page 8, line 7, after "means" insert -- a --;

line 8, change "are" to -- may be --;

line 12, change "are" to -- may be --.

Page 9, line 16, after "Following" insert -- the --.

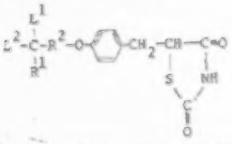
Page 10, line 2, after "following" insert -- the --.

Page 12, line 1, after "following" insert -- the --.

In the Claims:

Cancel Claims 1, 3, 4 and 7 and substitute the following Claims therefor:

10. A thiazolidine derivative of the formula:



wherein R^1 is a pyridyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, or a thiazolyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring; R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is hydrogen, lower alkyl or L^1 and L^2 are combined to form an alkylene group.

11. A thiazolidine derivative as claimed in Claim 10, each of L^1 and L^2 is hydrogen.

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Bi Canceled

3
12. A thiazolidine derivative as claimed in Claim 10, wherein R^2 is a lower alkylene group having 1 to 3 carbon atoms.

4
13. A compound as claimed in Claim 10, wherein the compound is 5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione.

5
14. A compound as claimed in Claim 10, wherein the compound is 5-[4-[2-(4-methyl-5-thiazolyl)ethoxy]benzyl]thiazolidine-2,4-dione.

15. A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in Claim 10.

REMARKS

The present Preliminary Amendment is submitted in an effort to place the application in optimum form for examination purposes.

The Specification has been amended to correct minor grammatical errors therein, which amendments are precisely the same as those presented in the previous applications including Serial No. 396,093.

In respect to the Claims, these Claims are essentially directed to the case wherein R^1 is a pyridyl group or a thiazolyl group which has 1 to 3 substituents on the rings of the pyridyl and thiazolyl groups, said substituents selected from lower alkyls, halogens and hydroxyl. Support for these substituents may be found on Page 3 of the Specification.

SA24

Claims 11 and 12 are simply narrowed embodiments restricting the L^1, L^2 and R^2 groups to cover preferred embodiments.

The compounds of Claims 13 and 14 are specifically disclosed in Example 9 of the original Specification as Compound Nos. 42 and 45, respectively.

In connection with the above, it must be pointed out that a Restriction Requirement was required in the first filed Kawamatsu application, Serial No. 62,512, now USP 4,287,208 in Paper No. 6 of that application. One of the groups of compounds restricted out is the case where R^1 represents pyridyl or thiazolyl and these compounds were claimed in USP 4,340,605, which was a divisional of the first filed application. However, in respect to the latter patent, it appears that the Claims do not cover the case wherein the pyridyl or thiazolyl groups may be substituted as disclosed in the original application. In this connection, as it turns out, the compounds in which these heterocyclic rings are substituted have become important, especially Compound 42 in Example 9.

In a brief discussion with the Examiner handling the parent application, it was thought best to file a Divisional application as has been done herein and to possibly file a Terminal Disclaimer at a later date.

It is respectfully requested that the present amendment be entered and be allowed. A Terminal Disclaimer will undoubtedly be required and will be filed at a later date, if necessary.

Respectfully submitted,

YUTAKA KAWAMATSU ET AL.

By John T. Pedigan
John T. Pedigan
Registration No. 24387
Attorney for Applicants

JTP/njp
Washington, D.C.
Tel. (202) 393-5150
March 15, 1983

SA25

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10/18/83
P. Webster

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

P. Webster 10/18/83

In re Application of

YUTAKA KANAMATSU ET AL.

Serial No. 476,017 — Group Art Unit 122

Filed March 15, 1983 — Examiner N. Rizzo

THIAZOLIDINE DERIVATIVES

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C.

Sir:

In response to the Official Action of July 8, 1983, kindly amend the above-identified application as follows:

In the Claims:

Amend Claim 15 as follows:

C1

~~15.~~ (amended) A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in ~~claim 14~~ and a pharmaceutically acceptable carrier therefor.

REMARKS

Further and favorable reconsideration is respectfully requested.

Claim 15 has been amended by stipulating that a "pharmaceutically acceptable carrier" is included in the composition claim. Support for this amendment is evident from the whole tenor of the Specification. Note, for example, Pages 4 and 5 of the Specification. By this amendment to the Claims, it is deemed that the rejection of Claim 15 in failing to point out the "other" components of the composition has been overcome.

SA26

The rejection of Claims 10-15 on the ground of double patenting over U.S.P. 4,340,605 is respectfully traversed.

In order to overcome this rejection, a Terminal Disclaimer is enclosed herewith, thereby overcoming any extension of monopoly, which is the chief concern in such double patenting rejection. In a recent telephonic interview, the Examiner indicated that such Terminal Disclaimer should overcome this rejection.

The Claims have been rejected under 35 USC 112 as not claiming the invention primarily on the basis that no clear support for the substituted compounds now claimed exist in the Specification. In this connection, R^1 has been claimed as being a pyridyl group or a thiazolyl group containing a narrow group of constituents selected from lower alkyls, haloyens and hydroxyl. Full support for this claim language may be found on Page 3 of the Specification.

In respect to the compounds numbered 13 and 14, these compounds are specifically disclosed in Example 9 of the original Specification as compound numbers 42 and 45, respectively. Thus, full support for Claims 13 and 14 may be found in the Specification.

In respect to the Examiner's contention that no clear support for the substituted compounds can be found in the Specification, this has been rebutted by a reading of the specific examples as pointed out above. Moreover, it is well established that each and every member of a Markush grouping need not be set forth by way of specific examples, especially when the Markush group grouping, i e. the substituents in this case, actually cover a relatively narrow and well defined group of constituents. Moreover, there should

no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic agent as specified in the instant disclosure. See In re Marzocchi et al. 169 USPQ 367.

In discussing this application with the Examiner to clarify matters, it was indicated that the above arguments, coupled with the Terminal Disclaimer and amendment to Claim 15 would undoubtedly place the application in allowable form. Accordingly, allowance of the application is respectfully solicited.

Respectfully submitted,

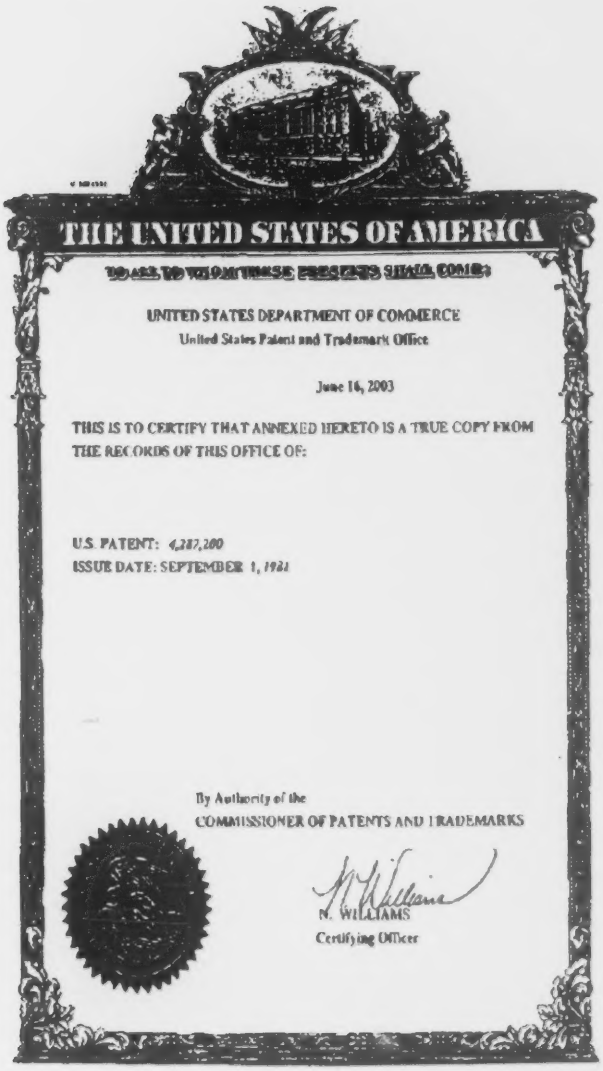
YUTAKA KAWAMATSU ET AL.

By John T. Fedigan
John T. Fedigan
Registration No. 24347
Attorney for Applicants

JTF/ajp
Washington, D.C.
Tel. (202)393-5150
September 13, 1983

A check covering the Patent Office fee of $50.00 for filing the enclosed Terminal Disclaimer accompanies this response.

SA28



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June 16, 2003

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 4,287,200
ISSUE DATE: SEPTEMBER 1, 1981

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WILLIAMS
Certifying Officer

SA29

United States Patent [19]

Kawamura et al.

[11] 4,287,200

[45] Sep. 1, 1981

[54] THIAZOLIDINE DERIVATIVES

[75] Inventors: Takeo Kawamura, Kyoto; Takeshi Fujita, Takarazuka, both of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 64,511

[22] Filed: Jul. 27, 1979

[30] Foreign Application Priority Data

Aug. 4, 1978 [JP] Japan 53-95473

[51] Int. Cl.³ C07D 277/04

[52] U.S. Cl. 424/270; 548/183; 546/194; 548/202

[58] Field of Search 548/183, 202; 424/270

[56] References Cited

U.S. PATENT DOCUMENTS

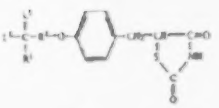
3,823,153 7/1974 Dimond et al. 548/183

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

Thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group containing one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur or a group of the formula

(wherein R^3 and R^4 are the same or different and each a lower alkyl or R^3 and R^4 are combined to each other either directly or as interrupted by a hetero atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring); R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each a lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen, respectively] are novel compounds and useful as, for example, remedies for diabetes, hyperlipemia and so on of mammals including human beings.

8 Claims, No Drawings

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THIAZOLIDINE DERIVATIVES

This invention relates to novel thiazolidine derivatives having hypolipidemic and hypoglycemic activities and low toxicity. More particularly, this invention relates to thiazolidine derivatives of the general formula:

(I)

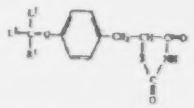
[wherein R' is alkyl, cycloalkyl, phenylalkyl, phenyl, a free- or an unreduced heterocyclic group including one or two hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, or a group of the formula

(where R' and R'' are the same or different and each means lower alkyl or R' and R'' are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring as taken together with the nitrogen atom adjacent to R' and R''; R' is a bond or a lower alkylene group; L' and L'' may be the same or different and each is lower alkyl or L' and L'' are combined to each other to form an alkylene group, provided that when R' is other than alkyl, L' and L'' may further be hydrogen, respectively].

Referring to the general formula (I), the alkyl group R' may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; the cycloalkyl group R' may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl; and the phenylalkyl group R' may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R' may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R' is

the lower alkyls R' and R'' may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and n-butyl. When R' and R'' are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, it is the form of

this heterocyclic group may further include a hetero-atom selected from among nitrogen, oxygen and sulfur, as exemplified by piperidine, morpholine, pyrrolidine and piperazine. The lower alkylene group R' may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene. The bond R' is equivalent to the symbol "-", "=" or the like which is used in chemical structural formulas, and when R' represents such a bond, the compound of general formula (I) is represented by the following general formula (II):



(II)

Thus, when R' is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L' and L'', there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L' and L'' are joined together is a group of the formula —$(CH_2)_n$— [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, as well as said heterocyclic group

may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.), lower alkoxy groups (e.g. methoxy, ethoxy, etc.), halogens (e.g. chlorine, bromine, etc.) and hydroxyl. The case also falls within the scope of the general formula [I] that an alkylenedioxy group of the Formula —O—$(CH_2)_m$—O— [m an integer of 1 to 3], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The compound (I) according to this invention can be converted to various salts by procedures known per se. For example, when the heterocyclic group R' includes a tertiary nitrogen atom, or R' means a group of the formula

the compound (I) can be converted to acid salts with acids, such as hydrochloric acid, sulfuric acid, acetic acid, oxalic acid, etc. When R' does not include a tertiary nitrogen atom, the compound may be converted to

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SA31

salts with cations such as a sodium ion, a potassium ion, a calcium ion, or an ammonium ion, etc.

The thiazolidine derivative (I) according to this invention has activity to lower the blood sugar and triglyceride levels in mice (KK-Ay) with spontaneous diabetes and is expected to be of value in the treatment of hyperlipemia, diabetes and their complications in mammals including human beings. The compound (I) has low toxicity. For example, the LD_{50} value of 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione in a rat is more than 10 g/kg. (P.O.). The compound (I) may be orally administered in such dosage forms as tablets, capsules, powders, granules, etc. or by other routes in such forms as injections, suppositories, pellets and so on. Taking the treatment of hyperlipemia as an example, the compound may be orally or otherwise administered at a normal daily dose level of 50 mg to 1 gram per adult human. For the treatment of diabetes, the compound (I) may be orally or otherwise administered at a normal daily dose of 10 mg to 1 gram per adult human.

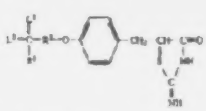
The thiazolidine derivative (I) of this invention may be produced, for example, by the following methods.

(1) The thiazolidine derivative (I) can be produced by the steps of reacting a compound of general formula (III) with thiourea to obtain an 2-iminothiazolidine derivative of general the formula (IV) and, then, hydrolyzing the last-mentioned derivative (IV).

(III)

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore; X^1 means halogen (e.g. chlorine, bromine, etc.), alkylsulfonyloxy (e.g. methylsulfonyloxy, etc.) or arylsulfonyloxy (e.g. toluenesulfonyloxy, etc.); Z is lower alkoxy (e.g. methoxy, ethoxy, etc.), hydroxyl, amino or a group of the formula —OM (M is, for example, an alkali metal atom, e.g. Na, K, etc., or NH_4)]

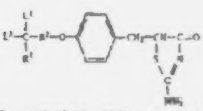
(IV)



[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore]

The compound (IV) may tautomerically take the form as below:

(IV)

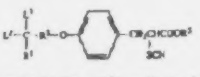


[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore] The compound (IV) is also included within the scope of this invention. In this specification, the nomenclature and formula of these compounds are described en bloc as "2-iminothiazolidine derivative" and as formula (IV), respectively.

The reaction between a compound (III) and thiourea is normally conducted in a solvent. As examples of such solvent may be mentioned alcohols (e.g. methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.), acetone, dimethylsulfoxide, sulfolane, dimethylformamide, etc. While the relative amounts of starting materials need not be critically controlled, it is normally desirable to employ a slight excess of thiourea based on compound (III). Thus, 1 to 2 molecular equivalents of thiourea is preferably employed relative to compound (III). While the conditions of reaction such as reaction temperature and time depend on such factors as the starting material, solvent, etc., the reaction is normally carried out at the boiling point of the solvent used or at 80° to 150° C. for a few to ten and odd hours. The sparingly soluble imino-compound (IV) is produced in the above manner. This imino-compound (IV) may be isolated prior to the following hydrolysis step or the reaction mixture containing (IV) may be directly hydrolyzed. In the hydrolysis step, the imino-compound (IV) is heated in a suitable solvent (e.g. sulfolane) and in the presence of water and mineral acid. The acid just mentioned is added normally in a proportion of 0.1 to 10 molecular equivalents, preferably 0.2 to 3 equivalents, based on compound (III), while water is used normally in large excess based on compound (III). The heating time normally ranges from a few hours to 10 and odd hours.

(2) The thiazolidine derivative (I) can further be produced by subjecting a compound of formula

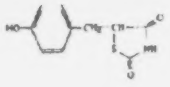
(V)



[wherein L^1, L^2, R^1 and R^2 have the meanings given above, and R^3 means alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, n-propyl, n-butyl, t-butyl, etc.), aryl having 6 to 8 carbon atoms (e.g. tolyl, etc.) or aralkyl having 7 to 8 carbon atoms (e.g. benzyl, etc.)] to a cyclization reaction. This cyclization reaction is usually carried out by hydrolyzing a compound (V) with water. The hydrolysis is generally conducted in the presence of a catalyst, examples of which include hydrogen halides (e.g. hydrogen chloride, hydrogen bromide), mineral acids such as hydrochloric acid, sulfuric acid, etc. The catalyst may generally be used in an amount of 20 to 50 mol equivalents relative to the compound (V). This reaction may be conducted in the presence of an organic solvent such as alcohol (e.g. methanol, ethanol, etc.). While the reaction temperature varies with the type of catalyst used, the reaction may generally be carried out at a temperature ranging 50° to 150° C. The reaction time is usually in the range of 2 to 30 hours.

(3) The thiazolidine derivative (I) can also be produced by reacting compound of the formula:

(VI)



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SA32

with a compound of the formula

(VII)

(wherein L^1, L^2, R^1 and R^2 have the meanings given above, and X^2 means a halogen atom such as chlorine, bromine, etc.) in the presence of a base. As the base, there may be mentioned sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. This reaction is usually carried out in the presence of a solvent. As a suitable solvent, there may be mentioned dimethylformamide, dimethylsulfoxide, etc. The reaction temperature may be in the range of room temperature to 100° C.

The resulting thiazolidine derivative (I) can be isolated and purified by conventional procedures such as concentration at atmospheric or subatmospheric pressure, solvent extraction, crystallization, recrystallization, phasic transfer, chromatography, etc.

The compound (VII) which is used as the starting material in the above preparation method (1) can be produced, for example, by the steps of diazotizing the corresponding aniline compound and subjecting the diazo-compound to Meerwein arylation.

The following reference and working examples are given to illustrate this invention in further detail.

REFERENCE EXAMPLE 1

In 200 ml of methanol is dissolved 19.0 g of 4-[2-(N,N-dibenylamino)ethoxy]nitrobenzene and after 3 g of 10% Pd-C (50% wet) is added, catalytic reduction is carried out at atmospheric temperature and pressure. The reaction system absorbs about 6.4 l of hydrogen in 75 minutes. The catalyst is then filtered off, the filtrate is concentrated under reduced pressure and the oily residue is dissolved in a mixture of 100 ml methanol and 100 ml acetone. Following the addition of 21.5 ml of concentrated hydrochloric acid, the solution is cooled to 0° C. and a solution of 4.9 g sodium nitrite in 10 ml water is added dropwise at a temperature not exceeding 5° C. The mixture is stirred at 5° C. for 20 minutes, at the end of which time 31.3 g (34.9 ml) of methyl acrylate is added. The reaction mixture is heated to 35° C. and 1 g of cuprous oxide is added in small portions, whereupon the temperature of the reaction system rises to 44° C. with the evolution of nitrogen gas. The mixture is stirred for one hour and after the temperature has dropped to room temperature, it is allowed to stand overnight. The solvent is then distilled off under reduced pressure and the residue is made strongly basic with concentrated aqueous ammonia. Then, following the addition of water, extraction is carried out with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate. The oily residue is chromatographed on a column of 300 g silica gel, elution being carried out with chloro-hexane (1:9), by the above procedure is obtained 10.7 g (44.8%) of ethyl 2-chloro-3-[4-[2-(N,N-dibenylamino) ethoxy]phenyl] propionate.

IR(liquid film) ν_{max}^{neat}: 2945, 2850, 1745, 1605, 1505, 1250, 1170, 1030

NMR δppm CDCl$_3$: 0.9-1.6(6H, t), 3.2-4.8(8H,m), 2.52(4H,s), 2.85(2H,t), 3.0-3.3(2H,m), 3.3(2H,s), 4.2(2H,s), 6.4(1H,s), 6.75-7.30(4H,q).

EXAMPLE 1

(a) A mixture of 3.6 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate, 0.73 g of thiourea and 3 ml of sulfolane is heated at 120° C. for 4 hours and after cooling, 15 ml of water is added. The oil is separated, ether is added to the oil and the crystalline insolubles (a) are separated from the solution (b) by filtration. The filtrate (b) is distilled to remove the solvent and the residue is run onto a column of 100 g silica gel, elution being carried out with chloroform. By the above procedure is obtained 1.7 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]-thiazolidine-2,4-dione. m.p. 107°-108° C. (benzene-ligroin)

On the other hand, crystals (a) are recrystallized from ethanol-acetone (3:1) to obtain 1 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidin-4-one with a decomposition point of 210°-213° C. A 300 mg portion of this crystalline product is boiled with 2 ml of sulfolane and 2 ml of 6 N-HCl at 170° C. for 5 hours. After cooling, 50 ml of water is added and the resulting crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 230 mg of 5-[4-(2-methyl-2-phenylpropyloxy) benzyl]thiazolidine-2,4-dione.

EXAMPLE 2

A mixture of 17 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl] propionate, 11 g of thiourea and 60 ml of sulfolane is heated at 110° C. for 6 hours and, then, boiled with 10 ml of 2 N-sulfuric acid (or 2 ml of 6 N-HCl) for 16 hours. After cooling, 1 l of water is added and the oil is separated and allowed to stand for a while, whereupon crystals separate out. These crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 19.9 g of 5-[4-(2-methyl-2-phenylpropyloxy) benzyl]thiazolidine-2,4-dione.

EXAMPLE 3

(a) 333 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy) phenyl]propionic acid and 150 mg of thiourea are heated with 2 ml of sulfolane at 120° C. for 1.5 hours and, following the addition of 2 ml of 6 N-HCl, the mixture is further heated for 5 hours, at the end of which time 10 ml of water is added. The resulting crystals are recovered by filtration. By the above procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(b) The same procedure as that described in (a) is repeated except that 355 mg of sodium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate are employed. By this procedure is obtained 330 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(c) The same procedure as that described in (a) is repeated except that 332 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionamide is employed. By the procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(d) In 10 ml of ethanol are dissolved 1.0 g of amino-2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]propionate and 0.8 g of thiourea and the solution is heated for 5 hours, at the end of which time 50 ml of water is added.

By the above procedure is obtained 1.6 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidin-4-one.

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SA33

EXAMPLE 4

In 7 ml of dimethylsulfoxide are dissolved 300 mg of 2-bromo-3-[4-(4-chlorobenzyloxy)phenyl]propionic acid and 100 mg of thiourea and the solution is heated at 110° C. for 1 hours. Then, after 0.5 ml of water is added, the solution is further heated for 5 hours. Then, 10 ml of water is added and the resulting crystals are recovered by filtration and recrystallized from benzene-n-hexane (1:1). By the above procedure is obtained 179 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 5

1.9 g Of ethyl 3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-3-(benzenesulfonyloxy)-propionate is dissolved in 20 ml of ethanol and to the solution 20 ml of 4 N hydrochloric acid is added. The reaction is refluxed for 24 hours. After cooling, water is added to the reaction mixture is subjected to extraction with ether. The extract is washed with water and then dried. After distilling off ether, the residue is crystallized from ether-n-hexane, whereby 730 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione is obtained.

EXAMPLE 6

2.1 g Of ethyl 2-methanesulfonyloxy-3-[4-(1-methyl-2-phenylpropyloxy)phenyl]propionate and 0.76 g of thiourea are added to 10 ml of sulfolane, and the mixture is heated at 110° C. with stirring for one hour. After adding 30 ml of 2 N—hydrochloric acid, the mixture is heated at 100° C. for 8 hours. After cooling, water is added to the mixture, and the mixture is subjected to extraction with ether. The extract is washed with water and dried. The ether is distilled off to give 1.3 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 7

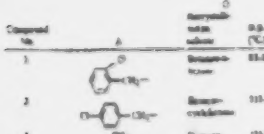
2.0 g Of ethyl 2-methanesulfonyloxy-3-[4-(1-methylcyclohexyloxy)phenyl]propionate and 760 mg of thiourea are added to 30 ml of ethanol. The mixture is refluxed for 2 hours. To the mixture is added 10 ml of hydrochloric acid, and the mixture is further refluxed for 16 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ethyl acetate. The extract is washed with water and dried. The ethyl acetate is distilled off to give 1.4 g of 5-[4-(1-methylcyclohexyloxy)benzyl]thiazolidine-2,4-dione. Crystallization from 85% ethanol gives crystals melting at 130°-131° C.

EXAMPLE 8

To 12 ml of dimethylsulfoxide is dissolved 1.12 g of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione, and 480 mg of 50% sodium hydride in oil is added to the solution. The mixture is stirred at room temperature for 15 minutes, to which is added 0.81 g of 4-chlorobenzyl chloride. The whole mixture is stirred at 50° C. for 4 hours. Water is added to the mixture and the mixture is acidified with 2 N - hydrochloric acid. The mixture is subjected to extraction with ether. The extract is washed with water and dried. Ether is distilled off to give an oily substance. The oily substance is subjected to column chromatography on 30 g silica gel, elution being carried out with cyclohexane-ethyl acetate (2:1). By the above procedure there was obtained 423 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 9

By procedures analogous to those described above in Examples 1 to 4, the following compounds were synthesized.



Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1		Benzene-n-hexane	88-89	1,3
2		Benzene-cyclohexane	115-116	3
3		Benzene-ligroin	110-120	1,3
4		Isopropyl ether	128-129	1
5		Ethanol-water	100-104	1,3
6		Cyclohexane	158-160	1

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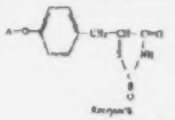
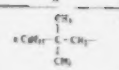
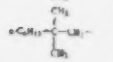
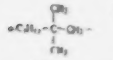
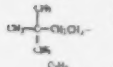
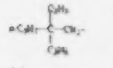
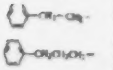
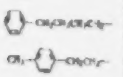
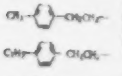
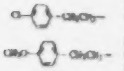
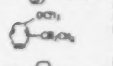
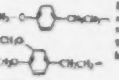
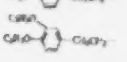
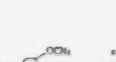
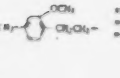
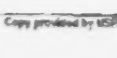


Example No.	R	Recrystallization solvent	m.p. (°C)	Analogous Example No.
7		Cyclohexane	108–110	2
8		Cyclohexane	109–111	2
9		Cyclohexane	107–109	2
10		Ethanol-benzene	106–108	1,2
11		n-Hexane	66–70	2
12		Benzene-ligroin	93–94	1,3
13		Ethyl acetate-cyclohexane	79–80	1
14		Ethyl acetate-cyclohexane	85–87	1
15		Ethyl acetate-cyclohexane	123–124	3
16		Ethanol-water	89–91	3
17		Ethyl acetate	146–148	3
18		Ethyl acetate-benzene	184–187	3
19		Ethanol-benzene	73–77	2
20		Ethyl acetate-n-hexane	103–104	2
21		Ethanol-benzene	110–111	2
22			Oil NMR(cm^{-1}): 3300, 1700, 1700, 1600 Reported Mw	2
23		n-Hexane-benzene	93–95	2

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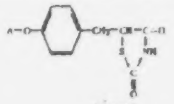
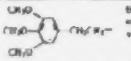
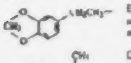
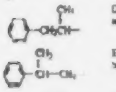
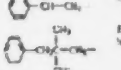
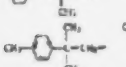
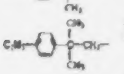
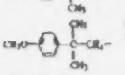
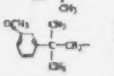
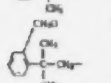
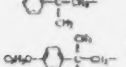
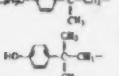
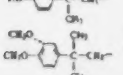
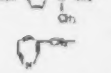
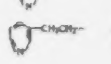


Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s)
21		Ethyl acetate-ether	108.5-109.5	1
22		Ethyl acetate-ether	132-133	1
23		Chloroform	84-85	1
24		Chloroform	66-67	1,3
25		Chloroform	182-184	1
26		Cyclohexane	106-107	1
27		Ethanol	104-120	1
28		Ethanol	109-120	1
29		Ethanol	65-69	1
30		Ethanol	116-117	1
31		Ethanol	77-80	1
32		Ether	137-138	3
33		Ethanol	120-122	1
34		Methanol	101-104	1
35		Chloroform-methanol	175-176	1,3

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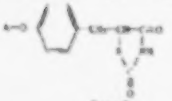
Continued



Compound No.	A	Recrystallisation solvent	m.p. (°C.)	Analogous Example No.
47		Chloroform/diethyl ether	128-131	1
48		[illegible]	209-210	1,3
49		Methanol	167-168	1
50		Ethyl acetate/diethyl ether	152-154	1
51		Ethanol/water	161-163	1
52		Ethanol	155-156.5	1
53		Cyclohexane	93-95	1
54		n-Pentane	120-122	1,3
55		Benzene/hexane	137-138	1,3
56		Cyclohexane	124-126	1,3
57		Ligroin	88-90	1
58		n-Hexane	85-87	1
59		Benzene/hexane	98-100	1
60		Ether/n-hexane	88-89	3
61		Ether/n-hexane	103-104	2

EXAMPLE 10

A mixture of 10.1 g. methyl 2-chloro-3-[4-(2-methoxyethoxy)phenyl]propionate and 6.64 g. thiourea is heated in the presence of 100 ml. of methanol at 120° C. for 4 hours. After cooling, a saturated aqueous solution of sodium hydrogen carbonate is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 6.1 g. (60.7%) of 2-amino-5-[4-(2-methoxyethoxy)benzyl]thiazolin-4-one is obtained as crystals. These crystals are recrystallized from ethyl acetate-methanol. Colorless needles, m.p. 159°-160° C.

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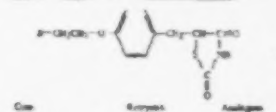
In 50 ml of 1 N - HCl is dissolved 4.1 g of the above 2-amino 5-[4-(2-morpholinoethyloxy)benzyl]thiazolidin-4-one and the solution is heated under reflux for 16 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 3.1 g (61.7%) of 3-[4-(2-morpholinoethyloxy)benzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from dimethylformamide-water. Colorless prisms, m.p. 189°–189° C.

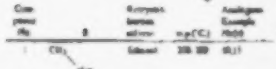
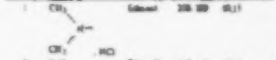
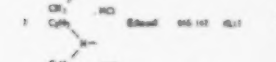
EXAMPLE 11

A mixture of 9.9 g methyl 2-chloro-3-[4-[2-(N,N-dimethylamino)ethyloxy]phenyl]propionate and 2.4 g thiourea is heated on the process of 100 ml of n-butanol at 100° C. for 15 hours. After cooling, the n-butanol is fractional off under reduced pressure, 100 ml of 2 N - HCl is added to the residue and the mixture is heated at 100° C. for 6 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over $MgSO_4$ and distilled to remove the ethyl acetate, whereupon 6.0 g (69.2%) of 5-[4-[2-(N,N-dimethylamino)ethyloxy]benzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from ethanol. Colorless prisms, m.p. 134°–135° C.

EXAMPLE 12

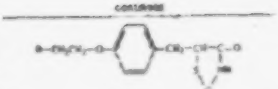
By procedures analogous to those described in Example 10 or 11, the following compounds were synthesized.



Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1	CH_3 	Ethanol	208–209	10,11
2	C_2H_5 	Ethanol	195–197	10,11
3	n-C_3H_7 	Ethanol	229–231	11
4	n-C_4H_9	Ethanol	230–232	11
5	n-C_5H_{11}	Ethanol	98–99	10,11
6	n-C_6H_{13}	Methanol	202–204	11

HCl

continued



Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
7		Methanol	240–242	11

HCl

EXAMPLE 13

An example of practical recipe in which the compound of the invention is utilized as remedies for diabetes is as follows.

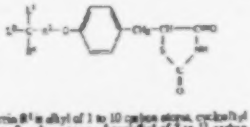
(Table)

(i)	Subject: carbon tetrachloride
	Particulate hydroxypropyl methylcellulose 2910 (Shin-Etsu Chemical Co., Ltd.)
	Lactose
	Corn starch
	Microcrystalline cellulose
	Magnesium stearate
	100 mg

(1), (2), (3) and 1 quantity of (4) are thoroughly mixed, and then the mixture is granulated. Remaining 1 quantity of (4), and (5) are added to the granules and compressed into tablets. Thus prepared tablets can be further coated with a suitable coating agent.

What is claimed is:

1. A thiazolidine derivative of the general formula



wherein R^1 is alkyl of 1 to 10 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenylalkyl of 7 to 11 carbon atoms, or phenyl; R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each a lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen.

2. A thiazolidine derivative as claimed in claim 1, wherein R^1 is an alkyl having 1 to 10 carbon atoms.

3. A thiazolidine derivative as claimed in claim 1, wherein L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms.

4. A thiazolidine derivative as claimed in claim 1, wherein R^2 is a lower alkylene group having 1 to 3 carbon atoms.

5. A thiazolidine derivative as claimed in claim 1, wherein R^1 is an alkyl having 1 to 10 carbon atoms, L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms, and R^2 is a lower alkylene group having 1 to 3 carbon atoms.

6. A thiazolidine derivative as claimed in claim 1, wherein the derivative is 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione.

7. A hypoglycemic and hypoglycemic pharmaceutical composition, which comprises, as active ingredient, the effective amount of a thiazolidine derivative defined in claim 1.

8. A hypoglycemic and hypoglycemic pharmaceutical composition as claimed in claim 1, wherein the derivative is 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione.

* * * * *

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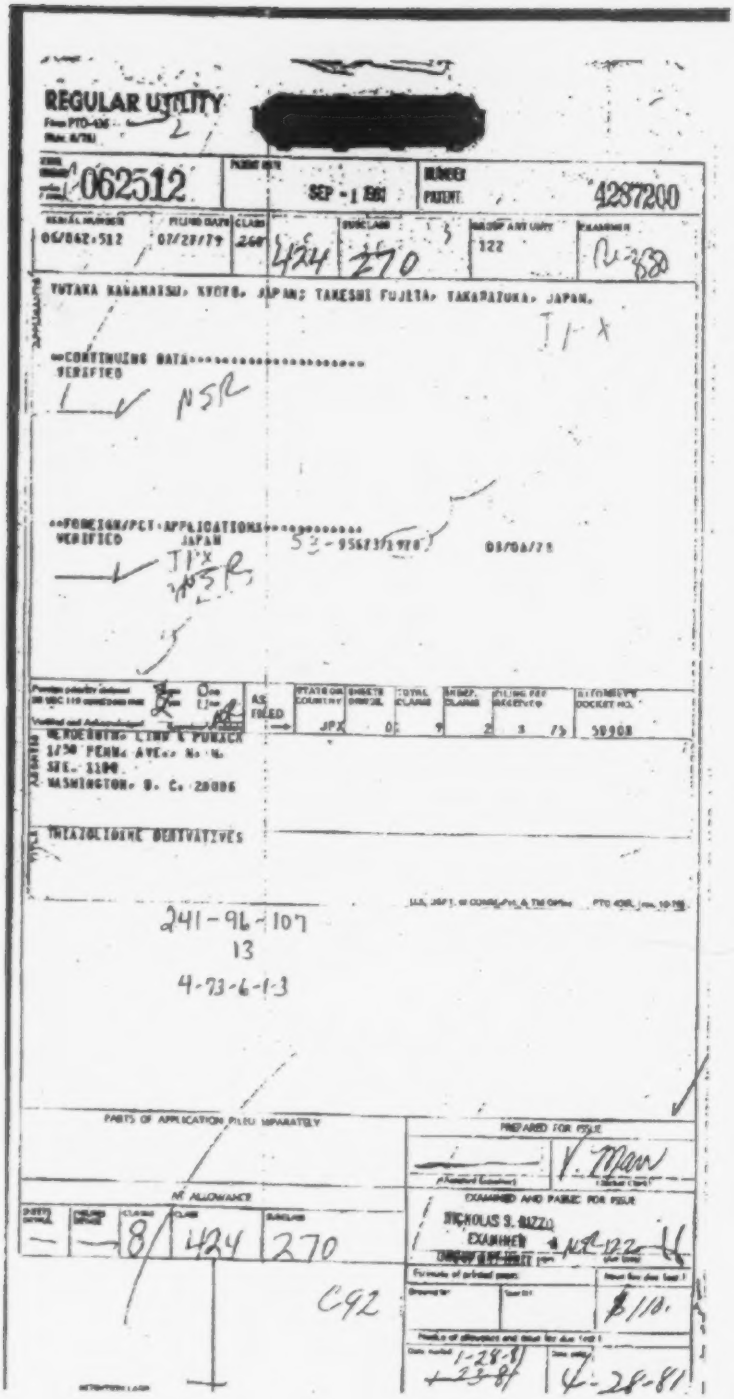

REGULAR UTILITY

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05/862,512 | 07/28/77 | 260 | 424 | 270 | 122

YUTAKA NAKANAISHI, KYOTO, JAPAN; TAKESHI FUJITA, TAKARAZUKA, JAPAN.

CONTINUING DATA

VERIFIED

FOREIGN/PCT APPLICATIONS

VERIFIED JAPAN 53-95873/1978 08/08/78

AS FILED | STATE OR COUNTRY JPX | SHEETS DRAWING 01 | TOTAL CLAIMS 9 | INDEP. CLAIMS 2 | FILING FEE RECEIVED 3 75 | ATTORNEY'S DOCKET NO. 50908

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1730 PENN. AVE., N. W.
SUITE 1100
WASHINGTON, D. C. 20006

THIAZOLIDINE DERIVATIVES

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4-73-6-1-3

PARTS OF APPLICATION FILED SEPARATELY

PREPARED FOR ISSUE

AT ALLOWANCE

8 | 424 | 270

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EXAMINED AND PASSED FOR ISSUE

NICHOLAS S. RIZZO
EXAMINER

$110.

1-28-81
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MAIL ROOM MAY 29 1980 U.S. PATENT AND TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

YUTAKA KAWAMATSU et al :

Serial No. 52,512 : Group Art Unit 122

Filed July 27, 1979 :

Thiazolidine Derivatives:

RECEIVED JUN 9 1980 GROUP 122

DECLARATION UNDER RULE 132

I, Takeshi Fujita, a citizen of Japan residing at 13-15, Nagaodai 1-chome, Takarazuka, Hyogo, Japan, sincerely declare;

That I was born on May 1, 1937 in Japan;

That I graduated from Faculty of Liberal Arts and Science, Shizuoka University in March, 1960;

That I received Master of Science degree for Biochemistry, from the Institute for Protein Research, Osaka University in March, 1962;

That I received Ph. D. degree for "Biochemical Studies on Bacterial Cytochromes", from the Institute for Protein Research, Osaka University in March, 1965;

That I have been an employee of Biological Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, Japan since April, 1965;

That I have engaged in the field of Biochemistry and Drug Metabolism in the laboratory of the said company;

That I have been Head of Biochemistry, Biological Research Laboratories since February, 1975;

That I have been a member of the Japanese Biochemical Society since 1960;

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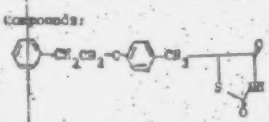
That the following experiments were carried out by my assistants under my direct guidance and supervision.

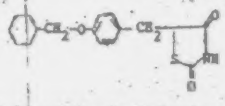
Experiment

Tests for blood glucose and lipid lowering effects

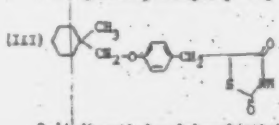
(1) Test Compounds:

(I) 

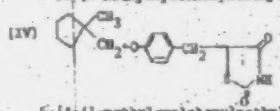
5-[4-(2-phenylethyloxy)benzyl]thiazolidine-2,4-dione

(II) 

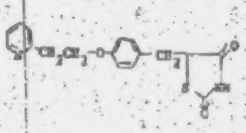
5-[4-cyclohexylmethyloxybenzyl]thiazolidine-2,4-dione

(III) 

5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione

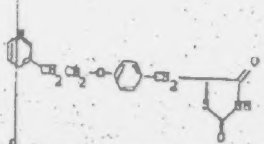
(IV) 

5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione

(V) 

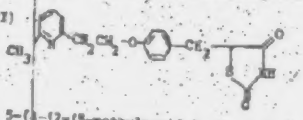
5-[4-[2-(2-pyridylethyloxy)]benzyl]thiazolidine-2,4-dione

(VI)



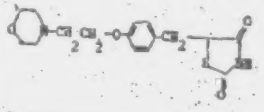
5-[4-[2-(3-pyridylethyloxy]benzyl)thiazolidine-2,4-dione

(VII)



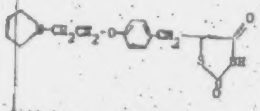
5-[4-[2-(5-methylpyrid-2-yl ethyloxy)]benzyl]thiazolidine-2,4-dione

(VIII)



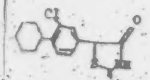
5-[4-(2-morpholinoethyloxy)benzyl]thiazolidine-2,4-dione

(IX)



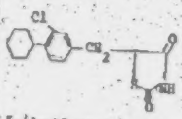
5-[4-[2-(1-pyrrolidinyl]ethyloxy]benzyl)thiazolidine-2,4-dione

(I)

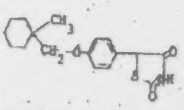


5-[3-chloro-4-cyclohexylphenyl)thiazolidine-2,4-dione

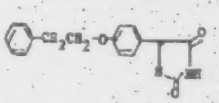
(II)



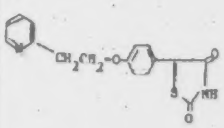
5-[3-chloro-4-cyclohexylbenzyl]thiazolidine-2,4-dione

(iii) 

5-[4-(1-methylcyclohexylmethyloxy)phenyl] thiazolidine-2,4-dione

(iv) 

5-[4-(2-phenylethyloxy)phanyl]thiazolidine-2,4-dione

(v) 

5-{4-[2-(2-pyridylethyloxy)]phenyl}thiazolidine-2,4-dione

(2) Animals employed in the tests:

Male genetically obese and diabetic mice, yellow KK, 8 to 10 weeks old.

(3) Test method:

The compounds to be tested were added to the powdered laboratory chow at levels shown in Table 1, and given to the mice for 4 days with free access to water. Blood samples were taken from the orbital vein. Fed blood glucose and plasma triglycerids were determined by the method of glucose oxidase and Fletcher, respectively.

SA43

(4) Result:

The results are shown in the following Table I.

Table I

Compounds	Dose (% in diet)	Blood Glucose ①	Plasma Triglyceride ①
I	0.02	29 *	27 *
II	0.02	38 ***	56 ****
III	0.07	45 ***	45 ***
IV	0.02	52 ****	47 ***
V	0.02	50 ***	47 ***
VI	0.02	51 ****	43 **
VII	0.02	50 ***	48 ****
VIII	0.02	52 ***	37 ***
IX	0.02	53 ***	37 ***
i	0.05	0	-21
ii	0.05	-1	-6
iii	0.1	-2	-91
iv	0.1	7	-21
v	0.05	-2	-6

(Note) Significant difference was ascertained with Student's t-test

*: $P<0.05$; **: $P<0.02$, ***: $P<0.01$, ****: $P<0.001$ VS control

①: % reduction from the control.

SA44

It is declared by the undersigned that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 8 th day of May, 1980.

Takeshi Fujita

Takeshi Fujita

SA45

(Chem. Pharm. Bull.)

Studies on Antidiabetic Agents. II.[1] Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives

TAKASHI SOHDA, KATSUTOSHI MIZUNO, KIKO IMAMIYA, YASUO SUGIYAMA, TAKESHI FUJITA, and YUTAKA KAWAMATSU*

Central Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

(Received April 22, 1982)

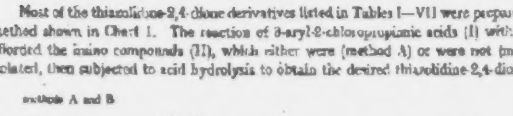
More than 100 5-substituted thiazolidine-2,4-diones were prepared and their hypoglycemic and hypolipidemic activities were evaluated with genetically obese and diabetic rats, yellow KK. The structure-activity relationship study showed that the 5-[4-oxybenzyl] moiety is essential for substantial activity. Among these compounds, 5-[4-(cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (47), 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (49, ADD-3878) and 5-[4-(2-(5-pyridyl)ethoxy)benzyl]thiazolidine-2,4-dione (59) exhibited the most favorable properties in terms of activity and toxicity.

Keywords—5-benzylthiazolidine-2,4-dione; hypoglycemic activity; hypolipidemic activity; genetically obese and diabetic rats (yellow KK); structure-activity relationship

In the preceding paper,[1] we reported that 5-[4-(2-methyl-2-phenylpropoxy)benzyl]-thiazolidine-2,4-dione (1, AL-321), prepared from ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate by reaction with thiourea followed by acid hydrolysis, had potent hypoglycemic and hypolipidemic activities. The present paper reports chemical modifications of the substituents at the 5-position of the thiazolidine ring in 1 and their effects on the pharmacological activities. 5-Benzylthiazolidine-2,4-diones bearing the 4-oxy group in the benzyl moiety, *i.e.*, 1—73, were prepared to investigate the structure-activity relationships. The synthesis and activities of 5-[4-aminobenzyl]- and 5-[2-alkoxy-5-pyridylmethyl]thiazolidine-2,4-dione derivatives, i.e., 74—83 and 92—101, respectively, are also described.

Chemistry

Most of the thiazolidine-2,4-dione derivatives listed in Tables I—VII were prepared by the method shown in Chart 1. The reaction of 3-aryl-2-chloropropionic acids (I) with thiourea afforded the imino compounds (II), which either were (method A) or were not (method B) isolated, then subjected to acid hydrolysis to obtain the desired thiazolidine-2,4-diones (III).



Ar = substituted phenyl, 2-alkoxy-5-pyridyl

Chart 1

Although the 3-aryl-2-chloropropionic acid derivatives (I) used in this reaction include esters, amides and sodium or ammonium salts as well as the free acids, the methyl or ethyl esters were mainly used in this study. Compounds III were also prepared by the methods shown in Chart 2 (methods C and D).[1,2]

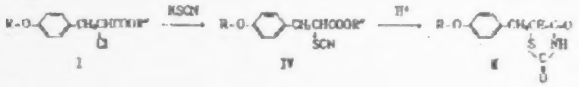


Chart 3

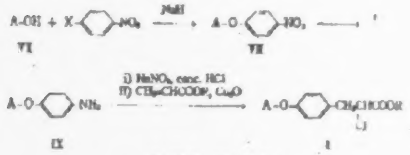


Chart 5

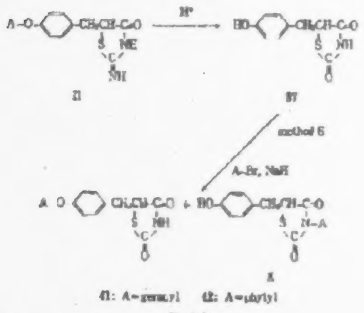


Chart 6

The starting compounds (I) with 4-oxy substituents were prepared by the general process shown in Chart 3, which includes the Meerwein arylation reaction (i.e., IX→I), as described previously.[1,2]

As shown in Chart 6, acid hydrolysis of the imino compound (II) bearing a geranyloxy or phytyloxy group resulted in concomitant cleavage of the ether linkage to yield a phenolic compound 87 (Table VI). Compounds 41 and 42 (Table III) were therefore prepared by *O*-alkylation of 87 (method E). In this method, the *N*-alkylated compound (X) was isolated as a by-product (Chart 6).

SA47

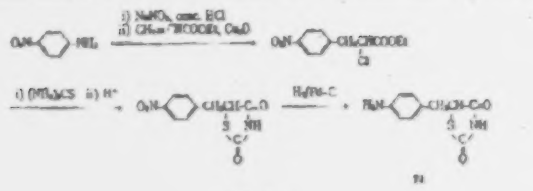


Chart 5

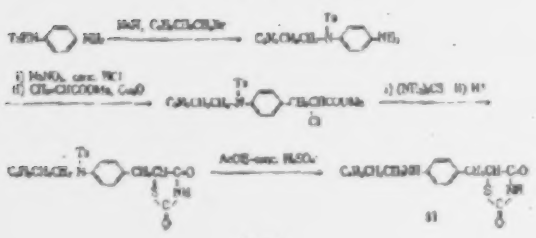


Chart 6

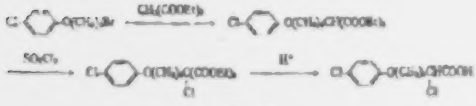


Chart 7

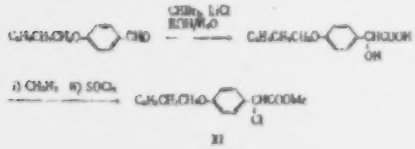


Chart 8

Compound 64 (Table IV) was prepared by concomitant hydrolysis of the 2-imino group on the thiazolidine ring and the *N*-benzoyl group on the pyrrolidine ring of the corresponding imino compound (II) (method *b*).

A series of compounds listed in Table V (except 81) was prepared from 74, which was derived starting from *p*-nitroaniline as shown in Chart 6.

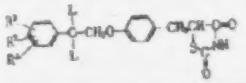
Appropriate acylation of 74 gave the corresponding 6-(4-acylaminobenzyl)thiazolidine-2,4-diones (76, 77 and 87). Reaction of 74 with *p*-toluenesulfonyl chloride, ethoxycarbonylmethylenecyanate and bis(2-chloroethyl)amine afforded 75, 80 and 83, respectively. Conden-

SA48

(R)$_n$ = 4-(CH$_3$)$_3$CCO-, 3,4-(CH$_3$O)$_2$-, 2,4,5-(C$_2$H$_5$O)$_3$-
R' = H, D
X = Cl, Br

Cont'd

TABLE 1. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	L	R^1	R^2	R^3	Method[a]	Yield[b] (%)	mp (°C)	Recrysta. solvent[c]	Formula[d]	Hypo glycemic activity[e]	Plasma triglyceride cholesterol-lowering activity[e]
1 (AL-321)	CH$_2$	H	H	H	A	88.7	110—111	Et-W	$C_{18}H_{17}NO_3S$	3	3
					B	89.6					
					C	72.5					
					D	78.4					
2	CH$_2$	4-CH$_3$	H	H	B	66.3	110—111	E-H	$C_{19}H_{19}NO_3S$	2	2
3	CH$_2$	2-CH$_3$O	H	H	B	77.6	116—117	E-H	$C_{19}H_{19}NO_4S$	3	3
4	CH$_2$	3-CH$_3$O	H	H	B	81.4	68—69	D-H	$C_{19}H_{19}NO_4S$	3	2
5	CH$_2$	4-CH$_3$O	H	H	B	58.1	107—108	E-E	$C_{19}H_{19}NO_4S$	1	2
6	CH$_2$	4-C$_2$H$_5$	H	H	B	85.7	104—105	D-H	$C_{20}H_{21}NO_3S$	3	1
7	CH$_2$	4-C$_3$H$_7$O	H	H	B	81.7	92—93	P-H	$C_{21}H_{23}NO_4S$	3	3
8	CH$_2$	4-OH	H	H	B	67.2	157—158	E	$C_{18}H_{17}NO_4S$	3	3
9	CH$_2$	3-CH$_3$O	4-CH$_3$O	H	B	80.4	106—107	E-H	$C_{20}H_{21}NO_5S$	3?	1?
10	H	H	H	H	B	69.2	93—94	B-E	$C_{17}H_{15}NO_3S$	3	4
11	H	4-CH$_3$	H	H	B	77.8	120—121	EA-H	$C_{18}H_{17}NO_3S$	3	2
12	H	3-CH$_3$O	H	H	B	89.3	73—75	A-H	$C_{18}H_{17}NO_4S$	3	4
13	H	4-CH$_3$O	H	H	B	71.0	104—105	EA-H	$C_{18}H_{17}NO_4S$	3	3
14	H	4-C$_2$H$_5$	H	H	B	78.5	87—88	E-H	$C_{19}H_{19}NO_3S$	3	2
15	H	4-C$_3$H$_7$O	H	H	B	79.5	102—103	EA-H	$C_{21}H_{23}NO_4S$	3	4
16	H	4-Cl	H	H	B	87.7	148—149	EA	$C_{17}H_{14}ClNO_3S$	3	3
17	H	3-CH$_3$O	4-CH$_3$	H	B	75.9	88—90	EA-H	$C_{19}H_{19}NO_4S$	3	3
18	H	3-CH$_3$O	4-CH$_3$O	H	B	70.0	110—111	EA-E	$C_{19}H_{19}NO_5S$	3	4
19	H	3-CH$_3$O	4-CH$_3$O	5-CH$_3$O	B	43.9	109—110	EA-H	$C_{20}H_{21}NO_6S$	3	2
20	H	3,4-OCH$_2$O		H	B	73.1	132—133	EA-H	$C_{18}H_{15}NO_5S$	3	3

a) See "Experimental".

b) Overall yield from the corresponding 3-haloketone (Ia: 1-one (II), [and ref. 4]), 3-chloro-4-oxybutanoate ester (R) (method B), 3 and 5 chloroacetophenone (IV) (method C) or 4-bromo-5-oxypentanoate (V) (method D).

c) A=acetone, B=C$_2$H$_5$, C=CHCl$_3$, Cy=cyclohexane, E=ETOH, H=hexane, D=diisopropyl ether, L=ligroin, M=MeOH, P=petroleum ether, Pr=propanol, W=H$_2$O.

d) All compounds were analyzed for C, H and N, and their results obtained for these elements were within ±0.4% of the calculated values.

e) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 5 mg/kg/day in the diet were calculated as percentage with respect to the control value; 70—80%, reduction=3, 50—69%, reduction=2, 30—49%, reduction=1, 30—
0%, reduction=0, 30—99%, reduction=-1, less than 9%, reduction=-2

f) The dosage 5 mg/kg/day

SA49

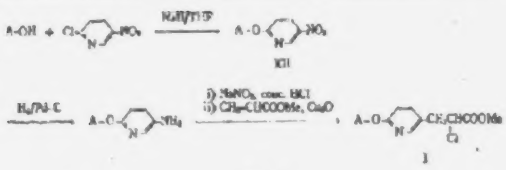
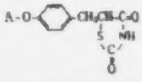


Chart 10

TABLE II. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[c]	Yield[d] (%)	mp (°C)	Recrystn. solvent[e]	Formula[f]	Hypoglycemic activity[g]	Plasma triglyceride-lowering activity[g]
31	C_6H_5-	B	93.4	119—119	B-H	$C_9H_9NO_2S$	1	1
10	$C_6H_5(CH_2)_2CH_2$-						3	4
32	$C_6H_5CH_2CH_2CH_2$-	B	48.9	79—80	EA-Cy	$C_{12}H_{13}NO_2S$	2	1
		C	75.6					
33	$C_6H_5CH_2CH(CH_3)CH_2$-	B	36.4	83—83	EA-Cy	$C_{13}H_{15}NO_2S$	2	1
34	$C_6H_5CH(CH_3)CH_2$-	B	78.5	Oil[h]	—	$C_{12}H_{13}NO_2S$	3	2
35	$C_6H_5CH_2CH(CH_3)$-	B	78.7	84—85	E-H	$C_{12}H_{13}NO_2S$	3	3
1	$C_6H_5(CH_2)_3CH_2$- (AL-321)						3	3
36	$C_6H_5CH_2C(CH_3)_2CH_2$-	B	85.8	107—108	EA-H	$C_{13}H_{15}NO_2S$	3	2
		C	71.1					
37	$(C_6H_5)_2CHCH_2$-	B	77.9	163—163	Et	$C_{18}H_{17}NO_2S$	1	1
38	$(C_6H_5)_2C(CH_3)CH_2$-	B	80.8	Oil[h]	—	$C_{19}H_{19}NO_2S$	2	3
39		B	91.0	126—127	D-E	$C_{16}H_{19}NO_3S$	5	1
40	3-Cl-C_6H_4-	D	44.6	89—90	EA-H	$C_{15}H_{10}ClNO_2S$	2	1
41	4-Cl-$C_6H_4CH_2$-	B	64.7	135—136	B-Cy	$C_{17}H_{14}ClNO_2S$	2	2
42	2-Cl-C_6H_4-CH_2-	B	93.0	85—86	D-H	$C_{17}H_{14}ClNO_2S$	3	2
43	3,4-$(OCH_2)_2$-$C_6H_3CH_2$-	B	44.9	178—177	C	$C_{13}H_{13}NO_4S$	1	1

a—c) See the corresponding footnotes in Table I.
f) Purified by silicone chromatography.

sation of 74 with *N*-protected ω-aminoalkanoic acids by the mixed anhydride method followed by deprotection yielded 78 and 79 (see "Experimental"). Compound 81 was prepared by the method illustrated in Chart 6.

2-Chloro-6-(4-chlorophenoxy)hexanoic acid required for the preparation of 84 was prepared by the method illustrated in Chart 7.

Methyl 2-chloro-2-(4-phenethyloxyphenyl)acetate (XI) required for the preparation of 85 (Table VI) was obtained from the corresponding aldehyde as shown in Chart 8.[6]

The starting 3-aryl-2-chloropropionic acids (I) for the preparations of 86 to 88 and 89 to 91 were obtained by the above-mentioned Meerwein arylation reaction of the corresponding aniline derivatives and the method shown in Chart 9, respectively.

A series of 5-(2-substituted-5-pyridylmethyl)thiazolidine-2,4-dione derivatives (92—101)

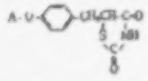
SA50

listed in Table VII was prepared by method B, and the starting 5 (5-alkoxy-6-pyridyl)-2-chlorocarboxylic acids (I) were prepared according to the route shown in Chart 10 using 2-chloro-6-nitropyridine.

Biological Method

Genetically obese and diabetic mice, yellow KK^{Ay} (male, 9 weeks old), were used. After prefeeding on a laboratory chow (CE-2, CLEA Japan) for 5 d, they were allocated to experimental groups of five mice each, so that the average blood glucose of each group was the same. The test compounds at 0.1% or 0.05% concentration, were mixed thoroughly with the powdered

Table III. Physical and Biological Properties of 5-(Substituted-benzyl)-2,4-dione Derivatives

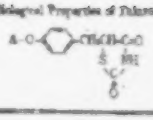


No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Fibrinogen uptake inhibitory activity[f]
34	$CH_3(CH_2)_4CH_2-$	B	51.3	58—66	EA–H	$C_{19}H_{29}NO_3S$	1	1
35	$(CH_3)_2CHCH_2-$	B	64.0	95—98	EA–H	$C_{18}H_{27}NO_3S$	1	1
36	$(CH_3)_3CCH_2-$	B	68.0	105—110	E–H	$C_{18}H_{27}NO_3S$	2	3
		C	73.5					
37	$ClCH_2CH_2CH(CH_3)CH_2-$	B	75.1	130—139	IPE	$C_{18}H_{26}ClNO_3S$	3	3
38	$CH_3(CH_2)_4CH(CH_3)CH_2-$	B	56.7	102—106	E–H	$C_{20}H_{31}NO_3S$	3	2
39	$CH_3CH_2CH(CH_3)CH_2-$	B	72.9	102—110	Cy	$C_{18}H_{27}NO_3S$	3	2
40	$CH_3(CH_2)_3CH(CH_3)CH_2-$	B	60.3	101—102	Cy	$C_{19}H_{29}NO_3S$	3	3
41	Geranyl-	B	30.0[g]	95—98	Cy–H	$C_{20}H_{29}NO_3S$	1	0
42	Phytyl-	B	49.9[g]	71—85	H	$C_{30}H_{49}NO_3S$	0	1
43	$CH_3CH=CH(CH_2)_3CH(CH_3)CH_2-$	B	75.6	98—100	Cy	$C_{20}H_{29}NO_3S$	2	0
44	Geranyl-$CH_2CH(CH_3)CH_2-$	B	78.4	Oil[h]	—	$C_{25}H_{41}NO_3S$	1	0
45		B	55.4	86—87	E–H	$C_{19}H_{23}NO_3S$	3	1
46		A	89.9	160—161	Eb–W	$C_{18}H_{21}NO_3S$	1[i]	1[i]
		D	77.5					
47		A	87.3	120—121	Py	$C_{19}H_{23}NO_3S$	2	3
48		D	67.1	62—67	Cy	$C_{20}H_{25}NO_3S$	3	2
49	(AHR-3010)	A	88.3	130—131	El	$C_{19}H_{23}NO_3S$	3	2
		B	87.3					
		C	78.2					
		D	90.9					
50		A	78.9	86—89	H	$C_{20}H_{25}NO_3S$	2	1
51		A	90.4	Oil[h]	—	$C_{20}H_{25}NO_3S$	3	3
52		A	80.2	127—128	B–L	$C_{19}H_{23}NO_3S$	3	3
53	Benzoyl-	A	69.5	153—154	Eb–W	$C_{19}H_{21}NO_4S$	2	2
54	Benzyl-	A	71.3	146—148	L	$C_{19}H_{23}NO_3S$	0	1
55	4-Methoxybenzyl-	A	87.4	93—98	H	$C_{20}H_{25}NO_4S$	1	1

a—c) See the corresponding footnotes in Table I. d) Unless noted otherwise, analyzed for C, H, N and/or S within ±0.4%. e) Determined by solvent chromatography. f) Test dosage 0.05% (w/w).

SA51

TABLE IV. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recryst. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[f]
58		D	69.6	183—186	C-M	$C_{16}H_{14}N_2O_3S$	3	3
59		B	78.4	209—210	DMF-W	$C_{17}H_{16}N_2O_3S$	3	2
60		B	62.7	160—164	EA-H	$C_{18}H_{18}N_2O_4S$ ·1/2H$_2$O	3	1
61		B	61.6	178—179	C-M	$C_{17}H_{16}N_2O_3S$	3*	2*
62		B	77.8	178—177	C-M	$C_{18}H_{18}N_2O_3S$	3	2
63		B	54.3	79—91	E-H	$C_{14}H_{14}NO_3S_2$	3	2
64		B	38.5	60—64	E-H	$C_{14}H_{13}NO_4S$	2	2
65		D	45.0	182—184	Th	$C_{14}H_{14}N_2O_3S_2$	2	3
66		F	33.3*	163—166	E-A	$C_{16}H_{18}N_2O_3S$·HCl	3	1
67	$(CH_3)_2CHNH$-CH_2CH_2-	D	62.9	228—231	M-E	$C_{16}H_{20}N_2O_3S$·HCl	1	1
68	$(CH_3)_2CHN$-CH_2CH_2-	B	57.9	205—211	E1	$C_{17}H_{22}N_2O_3S$·HCl	1	1
69	$C_6H_5CH_2N$-CH_2CH_2-	D	64.3	131—132	A-E	$C_{20}H_{20}N_2O_3S$·HCl	2	1
70	$C_6H_5CH_2N$-CH_2CH_2-	B	81.5	154—155	E	$C_{20}H_{20}N_2O_3S$	1	-
71	Bu-$C_6H_4CH_2N$-CH_2CH_2-	D	69.2	134—135	H	$C_{24}H_{28}N_2O_3S$	1*	2*
72		A	62.7	188—189	DMF-W	$C_{18}H_{16}N_2O_3S$	3*	2*
73		D	51.3	275—277	F1-W	$C_{17}H_{15}N_3O_3S$·2HCl·1/2H$_2$O	1	1
74		B	58.2	232—234	M	$C_{18}H_{17}NO_3S$·HCl	3	3
75		B	60.5	244—245	M	$C_{19}H_{19}NO_3S$·HCl	3	4

a—c) See the corresponding footnotes to Table I.

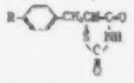
f) Ouabain used from acetate 1-(4-O-benzoyl-3-cyclohexylamino-2-propyl)-3-nitroguanidine (Table I).

g) The dosage 0.05% (w/w).

CE-2 diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from orbital vein. Blood glucose and plasma triglyceride were determined by the glucose oxidase method[10] and the method of Fletcher,[9] respectively. The maximum decreases of blood glucose and plasma triglyceride levels were calculated as percentage change from the control value.

SA52

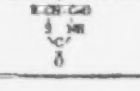
Table V. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	R	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride lowering activity[e]
74	H_2N-	88.9[f]	165—168	M	$C_{11}H_{10}N_2O_3S$	2	1
75	CH_3-(p-)-SO_2NH-	58.6	224—225	M	$C_{17}H_{16}N_2O_5S_2$	2	1
76	CH_3CH_2CONH-	95.8	148—151	EA	$C_{13}H_{14}N_2O_3S$	2	1
77	2-pyridyl-$CONH$-	36.8	271—272	DMF-W	$C_{15}H_{11}N_3O_3S$	1	1
78	$H_2NCH_2CH_2CONH$-	44.8	243—245	M	$C_{13}H_{15}N_3O_3S$·HBr	0	0
79	$H_2N(CH_2)_4CONH$-	47.0	216—218	DMF-E	$C_{15}H_{19}N_3O_3S$	0	0
80	$C_6H_5OCOCH_2NHCONH$-	58.7	161—162	H	$C_{18}H_{15}N_3O_5S$	0	0
81	$C_6H_5CH_2CH_2NH$-	63.4	156—157	A	$C_{18}H_{18}N_2O_3S$·HCl	1	1
82	Cl-(p-)-OCH_2-(m-)-$CONH_2$	98.4	221—222	M	$C_{18}H_{15}ClN_2O_4S$	2	0
83	HN(1)-R-	6.3	222—223	M	$C_{14}H_{14}N_2O_3S$·1/2H_2O	0	0

a) Yield from 76.
b—d) See footnotes (f, d) and e in Table 1, respectively.
e) Yield from 5-[p-(2-ethoxycarbonylethoxy)benzylidene]-2,4-dione.

Table VI. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives

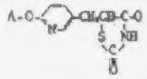


No.	R	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride lowering activity[e]
84	Cl-(p-)-$O(CH_2)_3$-		68.7[f]	95—96	EA-H	$C_{18}H_{16}ClNO_3S$	1	0
85	CH_3CH_2O-(p-)-		58.6[g]	119—120	EA-H	$C_{12}H_{13}NO_3S$	0	0
86	Cl-(p-)-CH_2-	B	38.5	130—131	E-H	$C_{10}H_8ClNO_2S$	0	0
87	HO-(p-)-CH_2-	B	60.7	159—160	EA-H	$C_{10}H_9NO_3S$	0	0
88	OCH_2-(p-)-CH_2-	B	47.5	133—134	EA-H	$C_{17}H_{13}NO_3S$	1	2
89	$(CH_3)_3CCO$-(p-)-CH_2-	B	64.6	175—174	Et	$C_{14}H_{17}NO_3S$	2	0
90	CH_3O-(3,4-)-CH_2- (CH_3O)	B	80.4	152—154	M	$C_{12}H_{13}NO_4S$	1	1
91	C_2H_5O-(3-)-OC_2H_5-(4-)-CH_2- (C_2H_5O)	B	81.4	108—106	EA-H	$C_{14}H_{17}NO_4S$	0	0

a—c) See the corresponding footnotes in Table 7.
f) Yield from 5-chloro-3-[4-(4-chlorophenoxybutoxy)benzylidene]-2,4-dione and.
g) Yield from methyl 5-(4-hydroxy-3-[5-ethoxy-2,4-dioxothiazolidin-5-ylmethyl]benzoate (XI).

SA53

Table VII. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride-lowering activity[d]
82	CH_3-	45.1	147—148	Et	$C_{19}H_{20}N_2O_3S \cdot HCl$	1[e]	1[e]
83		28.7	126—128	Pr	$C_{20}H_{22}N_2O_3S$	1[e]	1[e]
84	CH_3 CH_3-	47.3	141—142	Et	$C_{21}H_{24}N_2O_3S \cdot HCl$	3	2
85	CH_3CH_2-	41.2	89—97	E-PE	$C_{21}H_{24}N_2O_3S$	2	1
86	$(C_2H_5)_2N$-CH_2CH_2-	59.8	100—101	EA-H	$C_{25}H_{33}N_3O_3S$	1	1
87	N-CH_2CH_2-	39.6	149—152	Et	$C_{24}H_{24}N_2O_3S$	1[e]	1[e]
88	O N-CH_2CH_2-	41.6	209—213	C-M	$C_{28}H_{28}N_2O_5S$	1	1
89	CH_2CH_2-	36.8	75—77	EA-L	$C_{21}H_{21}NO_3S$	3	4
100	N CH_2CH_2-	54.5	165—170	M	$C_{20}H_{19}N_3O_3S$	5	2
101	N CH_2CH_2-	4.4	167—168	Et	$C_{20}H_{19}N_3O_3S$	5[e]	5[e]

a) Yield from the corresponding methyl 2-(2-alkoxy-5-methylbenzyl)-2-chloropropionate. Prepared by Method B.
b) The methods a, d or e in Table I, respectively.
c) The data of CHN (±0.4%).
d) Dose 0.03% (w/w).

Results and Discussion

The structures, physical constants and biological data of the thiazolidine-2,4-dione derivatives are shown in Tables I—VII.

Since compound 1 (AL-321) was first found to possess potent hypoglycemic and hypolipidemic activities,[1] various compounds having modified phenethyl moieties, as shown in Table I, have been synthesized. All the compounds, especially 12, 15 and 18, had pronounced hypoglycemic and hypolipidemic activities. Although slight potentiation of the biological activity was noted when the methyl groups on the side chain of 1 were removed (1 vs. 10), introduction of substituent(s) on the benzene ring of the phenethyl moiety did not alter the activities (1 vs. 2—9, 10 vs. 11—20).

Variation of the distance between the two benzene rings as listed in Table II indicated that the two-carbon unit was the most effective for eliciting the activity (1, 10, 24, 25>21, 23, 26; 16>31; 18>33).

Among the compounds listed in Tables I and II, compounds 10, 12, 15, 18 and 25 showed more potent activities than 1, but these compounds caused considerable increases in relative liver weight and liver lipid at high dose levels or on chronic administration. As this undesirable effect may have been a consequence of the existence of two benzene rings in the molecule, we replaced one of them with other moieties.

First, the phenethyl group of 10 was replaced by various alkyl groups. Such compounds, listed in Table III, exhibited good activities with reduced side effects. In particular, 40 (ADD-3878) showed a pronounced hypoglycemic effect and extremely low toxicity, though

SA54

its triglyceride lowering effect was not prominent. Compound 49 (ADD-3878) might therefore have potential utility as an antidiabetic drug. Compound 52 was as effective as but more toxic than 49 (ADD-3878). Compound 47 also showed good activities with low toxicity.

A series of compounds bearing less hypophilic groups (i.e., pyridylalkyl, aminoalkyl, etc.) instead of aralkyl or alkyl groups was next investigated. Although compounds 56, 57, 58, 59 and 63 in Table IV showed potent activities, they, especially 57 and 58, caused considerable increases in body weight and brown fat weight. Compound 70, 72 and 73 also exhibited potent activities, but had some side effects.

Besides these compounds, those listed in Tables V and VI were also prepared, but they exhibited no valuable activities. The fact that compounds 85 and 88 were completely or nearly inactive suggests that the partial structure is the essential structural feature for both glucose- and triglyceride-lowering activities.

Table VII lists compounds having a pyridine ring instead of the benzene ring in the 4-oxybenzyl group. These compounds, except 99 and 101, had weaker activities than the corresponding 4-oxybenzyl derivatives.

Conclusion

In a search for antidiabetic agents, we prepared a series of compounds related to thiazolidine-2,4-dione derivatives and evaluated their potential hypoglycemic and hypolipidemic activities in genetically obese and diabetic mice, yellow KK. Compounds 47, 49 (ADD-3878) and 59 exhibited the most favorable profiles in terms of activity and toxicity. These compounds may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity.

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian T-60 NMR spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard and coupling constants (J) are given in Hz. The following abbreviations are used, s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Nitro Compounds VIII and XII

Typical examples are given to illustrate the general procedure.

4-[2-(3-Methoxyphenyl)-2-methylpropoxy]nitrobenzene —A stirred mixture of 2-(3-methoxyphenyl)-2-methyl-1-propanol (10.9 g), *p*-chloronitrobenzene (8.8 g) and dimethylsulfoxide (DMSO) (100 ml) was treated portionwise with 50% NaH in oil (3.2 g) at 45°C. The mixture was stirred at 70°C for 80 min, poured into H_2O, acidified with 3 *n* HCl and extracted with Et_2O. The usual work-up gave crystals (12.7 g, 79.7%). Recrystallization from MeOH gave colorless prisms, mp 80—79°C. IR ν_{max}^{Nujol} cm^{-1}: 1510, 1340. NMR δ: 1.43 (6H, s), 3.78 (3H, s), 4.00 (2H, s), 6.6—7.6 (8H, m), 8.03 (2H, d, J=9), 8.17 (2H, d, J=9). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.37; N, 4.66.

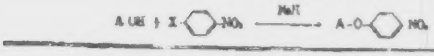
4-[2-(2-Pyridyl)ethoxy]nitrobenzene —A stirred and ice-cooled solution of 2-(2-pyridyl)ethanol (25.0 g) and *p*-fluoronitrobenzene (30.6 g) in dimethylformamide (DMF) (200 ml) was treated portionwise with 50% NaH in oil (19 g). The mixture was stirred with ice-cooling for 1 h and diluted with H_2O. The crystalline solid was filtered off and recrystallized from MeOH to give light yellow prisms (29.0 g, 58.5%), mp 76—77°C. IR ν_{max}^{Nujol} cm^{-1}: 1500, 1335. NMR δ: 3.27 (2H, t, J=7), 4.50 (2H, t, J=7), 6.90 (2H, d, J=9), 7.6—7.9 (3H, m), 8.13 (2H, d, J=9), 8.46 (1H, m). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.16; H, 4.92; N, 11.38.

The 4-alkoxynitrobenzenes (VIII) listed in Table VIII were similarly prepared. The unlisted compounds were reported in preceding papers.[8]

2-(2-Morpholinoethoxy)-5-nitropyridine —A stirred and ice-cooled solution of 2-chloro-5-nitropyridine (15.9 g) and 2-morpholinoethanol (13.1 g) in anhydrous tetrahydrofuran (THF) (200 ml) was treated portionwise with 60% NaH in oil (4.4 g). The mixture was stirred with ice-cooling for 1 h, diluted with H_2O (1 l) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give

SA55

Table VIII. Nitro Compounds (VIII)



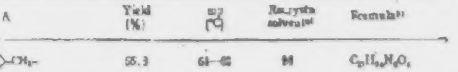
A	X	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
4-CH_3O-$C_6H_4C(CH_3)_2CH_2$-	Cl	80.6	78–79	M	$C_{20}H_{25}NO_3$
4-$C_{13}H_{27}$-$C_6H_4C(CH_3)_2CH_2$-	Cl	32.4	66–67	M	$C_{19}H_{23}NO_3$
4-$C_8H_{17}O$-$C_6H_4C(CH_3)_2CH_2$-	Cl	70.3	59–60	M	$C_{19}H_{23}NO_4$
4-$C_6H_5CH_2O$-$C_6H_4C(CH_3)_2CH_2$-	Cl	83.1	120–121	M	$C_{23}H_{23}NO_4$
3,4-$(CH_3O)_2$-$C_6H_3C(CH_3)_2CH_2$-	Cl	60.4	63–64	M	$C_{20}H_{25}NO_4$
4-CH_3-$C_6H_3CH_2CH_2$-	Cl	35.3	Oil	—	$C_{20}H_{25}NO_3$
2-CH_3O-$C_6H_3CH_2CH_2$-	Cl	58.9	91–92	M	$C_{20}H_{25}NO_4$
4-CH_3O-$C_6H_3CH_2CH_2$-	Cl	72.3	56–57	M	$C_{20}H_{25}NO_4$
4-C_6H_5-$C_6H_4CH_2CH_2$-	Cl	62.0	Oil	—	$C_{26}H_{27}NO_3$
4-C_6H_5O-$C_6H_4CH_2CH_2$-	F	77.9	85–87	M	$C_{26}H_{27}NO_4$
4-Cl-$C_6H_3CH_2CH_2$-	F	68.0	67–68	M	$C_{19}H_{21}ClNO_3$
2-CH_3O-4-CH_3-$C_6H_3CH_2CH_2$-	F	79.2	80–81	M	$C_{21}H_{27}NO_4$
3,4-$(CH_3O)_2$-$C_6H_3CH_2CH_2$-	Cl	66.9	93–94	M	$C_{21}H_{27}NO_5$
3,4,5-$(CH_3O)_3$-$C_6H_2CH_2CH_2$-	F	60.4	108–110	M	$C_{22}H_{29}NO_6$
3,4-(-OCH_2O-)-$C_6H_3CH_2CH_2$-	F	68.9	79–80	M	$C_{21}H_{25}NO_5$
$(C_6H_5)_2CHCH_2$-	F	89.0	132–133	Et	$C_{26}H_{27}NO_3$
$(C_6H_5)_2C(CH_3)CH_2$-	Cl	76.1	115–118	M	$C_{27}H_{29}NO_3$
	Cl	51.3	99–100	Et	$C_{20}H_{23}NO_3$
$CH_3CH_2C(CH_3)_2CH_2$-	Cl	86.0	Oil	—	$C_{15}H_{23}NO_3$
$CH_3(CH_2)_3C(CH_3)_2CH_2$-	Cl	73.9	Oil	—	$C_{16}H_{25}NO_3$
$CH_3(CH_2)_5C(CH_3)_2CH_2$-	Cl	57.9	Oil	—	$C_{18}H_{29}NO_3$
Geranyl-	Cl	36.5	Oil	—	$C_{20}H_{31}NO_3$
Phytyl-	F	79.5	Oil	—	$C_{36}H_{63}NO_4$
CH_2=CH-$CH_2C(CH_3)_2CH_2$-	Cl	74.2	Oil	—	$C_{15}H_{21}NO_3$
Geranyl-$C(CH_3)_2CH_2$-	Cl	61.2	Oil	—	$C_{20}H_{29}NO_3$
	F	78.1	Oil	—	$C_{20}H_{27}NO_3$
	F	75.0	Oil	—	$C_{20}H_{27}NO_4$
	F	75.5	77–78	M	$C_{20}H_{25}NO_4$
	Cl	62.0	67–68	M	$C_{21}H_{27}NO_4$
	Cl	86.5	59–60	Et–W	$C_{20}H_{31}NO_3$
	F	80.0	Oil	—	$C_{20}H_{27}NO_4$
	Cl	72.1	Oil	—	$C_{20}H_{29}NO_3$
	Cl	63.0	47–48	M	$C_{19}H_{27}NO_3$
Isobornyl-	Cl	78.5	100–110	M	$C_{20}H_{29}NO_3$
Dunnyl-	Cl	78.8	107–108	M	$C_{20}H_{29}NO_3$
l-Menthyl-	Cl	80.3	64–65	M	$C_{20}H_{29}NO_3$
	Cl	62.9	135–136	M	$C_{20}H_{18}N_2O_3$
	F	79.9	61–62	M	$C_{21}H_{20}N_2O_3$
	F	75.0	104–105	M	$C_{20}H_{18}N_2O_3$
	F	78.7	86–87	M	$C_{21}H_{20}N_2O_3$
	F	67.2	63–64	M	$C_{17}H_{17}NO_3S$

SA56

A	X	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
	F	57.2	52—54	M	$C_{20}H_{21}NO_4$
	F	85.6	93—95	M	$C_{20}H_{21}NO_3S$
	F	82.2	Oil	—	$C_{20}H_{23}N_3O_4$
$(CH_3)_2CHNH\text{-}CH_2CH_2$-	F	72.1	215—218	M–E	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(CH_3)_2NH\text{-}CH_2CH_2$-	F	70.5	241—244	M–P	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Cl	61.6	162—163	M–E	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Cl	71.0	Oil	—	$C_{20}H_{25}N_3O_4$
$(iso\text{-}C_3H_7)_2N\text{-}CH_2CH_2$-	Cl	67.2	Oil	—	$C_{22}H_{29}N_3O_4$
	F	82.4	82—83	EA–H	$C_{20}H_{23}N_3O_4$
	Cl	89.1	201—202	EA–W	$C_{20}H_{23}N_3O_4 \cdot HCl \cdot 2H_2O$
	Cl	93.3	195—196	EA–E	$C_{20}H_{23}N_3O_4 \cdot HCl$
	Cl	88.5	210—211	M–E	$C_{20}H_{23}N_3O_4 \cdot HCl$

a) E=Et$_2$O, EA=AcOEt, P=PrOH, M=MeOH, W=H$_2$O.
b) All compounds were analyzed for C, H and N, analytical results obtained for these elements were within ±0.4% of calculated values. Oily compounds were purified by column chromatography and used for the subsequent reactions.

Table IX. Nitro Compounds (XII)



A	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
	55.3	64—65	M	$C_{20}H_{24}N_2O_3$
	52.7	Oil	—	$C_{18}H_{20}N_2O_3$
	42.2	38—39	E–H	$C_{19}H_{22}N_2O_3$
	89.9	58—59	M	$C_{20}H_{24}N_2O_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	52.1	Oil	—	$C_{18}H_{25}N_3O_3$
	51.0	71—72	W	$C_{19}H_{23}N_3O_3$
	78.0	72—73	Et	$C_{20}H_{24}N_2O_3$
	75.5	56—57	E–H	$C_{19}H_{22}N_2O_3$
	80.2	116—117	M	$C_{19}H_{23}N_3O_3$

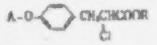
a, b) See the corresponding footnotes in Table VIII.

crystals (20.0 g, 79.1%). Recrystallization from EtOH gave light yellow prisms, mp 77—78°C. IR ν_{max}^{KBr} cm^{-1}: 1575, 1345. NMR δ: 2.60 (4H, t, J=6), 3.70 (4H, t, J=6), 4.64 (2H, t, J=6), 6.92 (1H, d, J=9), 8.41 (1H, q, J=9 and 3), 9.12 (1H, d, J=3). *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 58.17; H, 6.62; N, 16.69. Found: C, 58.21; H, 6.91; N, 16.47.

The 2-alkoxy-5-nitropyridines (XII) listed in Table IX were similarly prepared.

SA57

Table X. 3-Aryl-2-chloropropionic Acids (I)



A	R	Yield[a] (%)	Formula[b]
3-CH_3O-4-$C_6H_5CH_2O$-CH_2-	Me	54.0	$C_{17}H_{17}ClO_4$
4-CH_3O-3-$C_6H_5CH_2O$-CH_2-	Me	49.0	$C_{17}H_{17}ClO_4$
4-(2,4-F_2-C_6H_3)-CH_2-	Me	60.7	$C_{11}H_9F_2ClO_2$
4-C_6F_5O-C_6F_4-CH_2-	Me	49.7	$C_{16}H_7F_6ClO_3$
4-HO-3-CH_3O-C_6H_3-CH_2-	Et	46.0	$C_{12}H_{15}ClO_4$
3,4-(CH_2O_2)-C_6H_3-CH_2-	Me	50.0	$C_{11}H_{11}ClO_4$
4-CH_3-C_6H_4-CH_2-	Et	40.7	$C_{12}H_{15}ClO_2$
2-CH_3O-$C_6H_4CH_2$-	Me	41.6	$C_{11}H_{13}ClO_3$
4-CH_3O-$C_6H_4CH_2$-	Me	47.8	$C_{11}H_{13}ClO_3$
4-C_6H_5-$C_6H_4CH_2$-	Me	64.0	$C_{16}H_{15}ClO_2$
4-C_6H_5O-$C_6H_4CH_2$-	Me	51.7	$C_{16}H_{15}ClO_3$
4-Cl-$C_6H_4CH_2$-	Me	26.1	$C_{10}H_{10}Cl_2O_2$
2-CH_3O-, 4-CH_3-$C_6H_3CH_2$-	Me	60.9	$C_{12}H_{15}ClO_3$
2,4-(CH_3O)$_2$-$C_6H_3CH_2$-	Me	46.7	$C_{12}H_{15}ClO_4$
3,4,5-(CH_3O)$_3$-C_6H_2-CH_2-	Me	64.0	$C_{13}H_{17}ClO_5$
3,4-(-OCH_2O-)-$C_6H_3CH_2$-	Me	68.7	$C_{11}H_{11}ClO_4$
(C_6H_5)$_2$CH-CH_2-	Et	67.5	$C_{18}H_{19}ClO_2$
(C_6H_5)$_2$C(CH_3)-CH_2-	Et	78.0	$C_{19}H_{21}ClO_2$
	Et	78.5	$C_{20}H_{23}ClO_2$
C_6H_5-CH_2-	Et	63.3	$C_{13}H_{17}ClO_2$
$CH_3CH_2C(CH_3)_2CH_2$-	Me	60.9	$C_{13}H_{17}ClO_2$
$CH_3(CH_2)_2C(CH_3)_2CH_2$-	Et	64.1	$C_{15}H_{21}ClO_2$
$CH_3(CH_2)_3C(CH_3)_2CH_2$-	Et	58.8	$C_{16}H_{23}ClO_2$
Geranyl-	Et	60.3	$C_{18}H_{29}ClO_2$
Phytyl-	Et	56.0	$C_{24}H_{41}ClO_2$
CH_2=CH-$CH_2C(CH_3)_2CH_2$-	Et	58.8	$C_{15}H_{19}ClO_2$
Geranyl-$C(CH_3)_2CH_2$-	Et	54.0	$C_{20}H_{33}ClO_2$
	Me	77.1	$C_{10}H_{11}ClO_2$
	Me	75.6	$C_{10}H_{11}ClO_2$
	Me	78.5	$C_{11}H_{13}ClO_2$
	Me	73.2	$C_{12}H_{15}ClO_2$
	Et	76.7	$C_{13}H_{17}ClO_2$
	Me	78.1	$C_{13}H_{15}ClO_2$
Isobornyl-	Me	75.0	$C_{14}H_{21}ClO_2$
Bornyl-	Me	74.3	$C_{14}H_{21}ClO_2$
l-Menthyl-	Me	78.8	$C_{14}H_{25}ClO_2$
	Me	64.3	$C_{11}H_{10}ClNO_2$
	Me	61.2	$C_{12}H_{12}ClNO_2$
	Me	80.1	$C_{12}H_{11}Cl_2NO_2$
	Me	53.3	$C_{12}H_{12}ClNO_2$
	Me	63.8	$C_{13}H_{14}ClNO_2$

SA58

A	R	Yield[a] (%)	Formula[b]
	Me	72.7	$C_{20}H_{22}ClO_3S$
	Me	96.4	$C_{20}H_{22}ClO_3$
	Me	67.9	$C_{20}H_{23}ClNO_3S$
	Me	65.1	$C_{20}H_{20}ClNO_4$
$(CH_3)_2CHNH\text{-}CH_2CH_2$-	Me	37.8	$C_{17}H_{24}ClNO_3$
$(CH_3)_2CHN\text{-}CH_2CH_2$-	Me	48.3	$C_{18}H_{26}ClNO_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Me	53.6	$C_{18}H_{26}ClNO_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Me	53.5	$C_{18}H_{26}ClNO_3$
$(iso\text{-}C_3H_7)_2N\text{-}CH_2CH_2$-	Me	59.8	$C_{20}H_{30}ClNO_3$
	Me	45.1	$C_{19}H_{24}ClNO_3$
	Me	31.6	$C_{20}H_{25}ClN_2O_3$
	Me	48.1	$C_{20}H_{24}ClNO_3$
	Me	52.7	$C_{21}H_{26}ClNO_3$

a) Overall yield from the corresponding nitro compound (VIII).
b) All compounds were oily products and were purified by column chromatography on silica gel.

3-Aryl-2-chloropropionic Acids (I)

Typical examples are given to illustrate the general procedure.

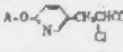
Methyl 2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate — A mixture of 4-(1-methylcyclohexylmethoxy)nitrobenzene (50.2 g), 10% Pd-C (2.0 g) and MeOH (400 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (500 ml). To this stirred and ice-cooled solution, conc. HCl (66 ml) and a solution of $NaNO_2$ (18.9 g) in H_2O (40 ml) were added dropwise below 5°C. The whole was stirred at 5°C for 30 min, then methyl acrylate (124 g) was added thereto and the temperature was raised to 25°C. Cu_2O (0.3 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (700 g) using Et_2O–hexane (1: 19, v/v) as an eluent to give a pure oil (51.8 g, 77.8%). IR ν_{max}^{film} cm^{-1}: 1745. NMR (C_6D_6) δ: 1.0 (3H, s), 1.30 (12H, br s), 2.80 (1H, q, J=14 and 7), 3.19 (1H, q, J=14 and 7), 3.34 (2H, s), 3.45 (3H, s), 4.30 (1H, t, J=7), 6.75 (2H, d, J=8), 6.98 (2H, d, J=8). The ester was converted to the corresponding acid by the usual alkaline hydrolysis in quantitative yield, mp 104—106°C (from hexane). IR ν_{max}^{Nujol} cm^{-1}: 1710. NMR δ: 1.0 (3H, s), 1.43 (12H, br s), 2.86 (1H, q, J=14 and 7), 3.31 (1H, q, J=14 and 7), 3.40 (2H, s), 4.19 (1H, t, J=7), 6.81 (2H, d, J=8), 7.19 (2H, d, J=8), 10.56 (1H, br s). *Anal.* Calcd for $C_{20}H_{29}ClO_3$: C, 68.09; H, 8.48. Found: C, 68.60; H, 7.30.

The 3-(4-alkoxyphenyl) 2-chloropropionates listed in Table X were similarly prepared. The related compounds were reported in preceding papers.[3]

Methyl 2-Chloro-3-[5-[2-(3-pyridyloxy)-3-pyridyl]-2-pyridyl]propionate — A mixture of 5-nitro-2-[2-(3-pyridyloxy)ethoxy]pyridine (15.0 g), 10% Pd-C (2.0 g) and MeOH (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, acetone (100 ml) was added to the filtrate. To the stirred and ice-cooled solution, conc. HCl (26 ml) and a solution of $NaNO_2$ (4.6 g) in H_2O (10 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min and methyl acrylate (35 g) was added thereto. The temperature was raised to 35°C and Cu_2O (1.0 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O, neutralized with conc. NH_4OH and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (150 g) using Et_2O–hexane–Et_3N (36: 35: 1, v/v) as an eluent to give a pure oil (1.5 g, 33.3%). IR ν_{max}^{film} cm^{-1}: 1736. NMR δ: 3.09 (2H, t, J=7), 3.0—3.5 (2H, m), 3.75 (3H, s), 4.63 (1H, t, J=7), 4.57 (2H, t, J=7), 6.75 (1H, d, J=8), 7.2—7.8 (5H, m), 8.02 (1H, d, J=2), 8.3—8.7 (2H, m).

SA59

Table XI. Methyl 3-(2-Alkoxy-4-pyridyl)-2-chloropropionates (I)



A	Yield[a] (%)	Formula[b]
	60.2	$C_{20}H_{20}ClNO_3$
	41.2	$C_{20}H_{20}ClNO_3$
	38.7	$C_{21}H_{22}ClNO_3$
	63.9	$C_{21}H_{22}ClNO_3$
	19.6	$C_{20}H_{19}ClN_2O_3$
	53.5	$C_{20}H_{21}ClN_2O_3$
	58.5	$C_{20}H_{21}ClN_2O_3$
	74.6	$C_{20}H_{19}ClNO_3$
	27.5	$C_{19}H_{19}ClN_2O_3$

a, b) See the corresponding footnotes in Table X.

The 3-(2-alkoxy-4-pyridyl)-2-chloropropionates listed in Table XI were similarly prepared.

Thiazolidine-2,4-diones (II)

Typical examples are given to illustrate the general procedure.

Method A——5-[4-[(1-Methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of 2-(p-iso-5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidin-4-one (8.0 g), 3 N HCl (10 ml) and 2-methoxyethanol (60 ml) was refluxed for 6 h, cooled and diluted with H_2O to give crystals of 49. Recrystallization from 85% EtOH gave colorless plates (5.3 g, 51.3%), mp 130—131°C. IR ν_{max}^{Nujol} cm^{-1}: 3100, 3050, 1780, 1645. NMR δ: 1.03 (3H, s), 1.47 (10H, br s), 3.08 (1H, q, J=14 and 9), 3.48 (1H, q, J=14 and 4), 3.47 (2H, s), 4.55 (1H, q, J=9 and 4), 6.52 (2H, d, J=9), 7.33 (2H, d, J=9), 8.12 (1H, br s). *Anal.* Calcd for $C_{24}H_{33}NO_3S$: C, 66.94; H, 6.98; N, 4.20. Found: C, 64.78; H, 6.88; N, 4.18.

The starting material used for this method was prepared as follows:

2-Imino-5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidin-4-one: A mixture of methyl 2-chloro-3-[4-[(1-methylcyclohexyl)methoxy]phenyl]propionate (13.2 g), thiourea (5.0 g), NaOAc (3.3 g) and 2-methoxyethanol (80 ml) was stirred at 100°C for 10 h and concentrated *in vacuo*. H_2O (50 ml)–hexane (50 ml) was added to the residue and the insoluble solid was filtered off (10.5 g, 80.4%). Recrystallization from EtOH gave colorless prisms, mp 263—264°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3210, 1685. NMR (d_6-DMSO) δ: 0.96 (3H, s), 1.40 (10H, br s), 2.70 (1H, q, J=14 and 9), 3.35 (1H, q, J=14 and 4), 3.62 (2H, s), 4.40 (1H, q, J=9 and 4), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 8.65 (1H, br s), 8.85 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.89; H, 7.39; N, 8.62. Found: C, 64.92; H, 7.31; N, 8.27.

The 2-iminothiazolidin-4-ones (II) listed in Table XII were similarly prepared.

Method B——5-[4-[2-(3-Methoxy-4-methylphenyl)ethoxy]benzyl]thiazolidine-2,4-dione (17): A mixture of methyl 2-chloro-3-[4-[2-(3-methoxy-4-methylphenyl)ethoxy]phenyl]propionate (12.0 g), thiourea (5.5 g) and sulfolane (150 ml) was stirred at 130°C for 10 h, then 2 N HCl (50 ml) was added thereto. The mixture was stirred at 100°C for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give 17 as crystals (10.5 g, 78.9%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 92—93°C. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1750, 1690. NMR δ: 2.14 (3H, s), 3.02 (1H, q, J=14 and 9), 3.05 (2H, t, J=7), 3.47 (1H, q, J=14 and 4), 3.80 (3H, s), 4.32 (2H, t, J=7), 4.45 (1H, q, J=9 and 4), 6.8—7.4 (7H, m), 9.45 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_4S$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.56; H, 5.59; N, 3.61.

Method C——5-[4-[(1-Methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of methyl 3-[4-[(1-methylcyclohexyl)methoxy]phenyl]-2-thioxopropionate (3.0 g), 6 N HCl (20 ml) and EtOH (20 ml) was refluxed for 60 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give 49 as crystals (1.38 g, 70.9%). Recrystallization from 85% EtOH gave colorless plates, mp 130—131°C. This sample was identical with an authentic sample of 49 prepared by method A.

SA60

TABLE XII 2-Imonothiazolidin-4-ones (II)

A	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
Geranyl-	54.9	189—190	A	$C_{20}H_{33}NO_2S$
Phytyl	62.9	173—174	A	$C_{30}H_{57}NO_2S$
	66.7	280—281[d]	Et	$C_{20}H_{29}NO_2S$
	78.0	253—254[d]	Et	$C_{20}H_{29}NO_2S$
	74.1	237—238[d]	Et	$C_{20}H_{29}NO_2S$
	72.0	233—234[d]	Et	$C_{20}H_{29}NO_2S$
	75.6	250—252[d]	Et	$C_{20}H_{29}NO_2S$
Isobornyl-	70.5	283—284[d]	Et	$C_{20}H_{33}NO_2S$
Bornyl-	80.6	280—282[d]	Et	$C_{20}H_{33}NO_2S$
l-Menthyl-	75.1	236—238[d]	Et	$C_{20}H_{33}NO_2S$
	50.0	191—192	EA–M	$C_{20}H_{31}NO_2S$

a) Yield from the corresponding 3-aryl-2-chloropropionic acid (I).
b) Rec.
c) A = acetone EA = AcOEt, Et = EtOH, M = MeOH.
d) All compounds were analyzed for C, H and N; analytical results obtained for these compounds were within 0.4% of calculated values.

The starting materials used for this method were prepared as follows.

Methyl 3-[4-[1-Methylcyclohexylmethoxy]phenyl]-3-thiocyanatopropionate: A mixture of methyl 3-chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate (8.35 g), potassium thiocyanate (1.46 g) and DMSO (35 ml) was stirred at 100°C for 3 h, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (8.18 g, 91.8%). Recrystallization from benzene gave colorless needles, mp 54—55°C. IR ν_{max}^{KBr} cm^{-1}: 2160, 1730. NMR δ: 1.00 (3H, s), 1.13 (10H, br s), 3.13 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.82 (2H, s), 3.78 (3H, s), 3.94 (1H, t, J=7), 6.88 (2H, d, J=9), 7.12 (2H, d, J=9). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.60; H, 7.36; N, 4.03. Found: C, 65.74; H, 7.47; N, 4.16.

The following compounds were similarly prepared.

Ethyl 3-[4-(3-Methyl-2-phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 90.8%. IR ν_{max}^{neat} cm^{-1}: 2160, 1735. NMR δ: 1.20 (3H, t, J=7), 1.63 (3H, s), 2.13 (1H, q, J=14 and 7), 3.22 (1H, q, J=14 and 7), 3.83 (1H, t, J=7), 3.90 (2H, s), 4.15 (2H, q, J=7), 6.82 (2H, d, J=9), 7.00 (2H, d, J=9), 7.2—7.6 (5H, m).

Ethyl 3-[4-(2,2-Dimethylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 83.4%. IR ν_{max}^{neat} cm^{-1}: 2165, 1735. NMR δ: 1.03 (9H, s), 1.30 (3H, t, J=7), 3.10 (1H, q, J=14 and 7), 3.35 (1H, q, J=14 and 7), 3.56 (2H, s), 3.92 (1H, t, J=7), 4.25 (2H, q, J=7), 6.82 (2H, d, J=9), 7.13 (2H, d, J=9).

Ethyl 3-[4-(3,3-Dimethyl-2-phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 80.0%. IR ν_{max}^{neat} cm^{-1}: 2160, 1735. NMR δ: 1.0 (6H, s), 1.33 (3H, t, J=7), 2.67 (2H, s), 3.10 (1H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 3.47 (2H, s), 3.80 (1H, t, J=7), 4.17 (2H, q, J=7), 6.77 (2H, d, J=9), 7.08 (2H, d, J=9), 7.10 (5H, br s).

Ethyl 3-[4-(3-Phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 88.1%. IR ν_{max}^{neat} cm^{-1}: 2165, 1736. NMR δ: 1.31 (3H, t, J=7), 1.9—2.4 (2H, m), 2.76 (2H, t, J=7), 3.14 (1H, q, J=14 and 7), 3.21 (1H, q, J=14 and 7), 3.85 (2H, t, J=7), 3.99 (1H, t, J=7), 4.14 (2H, q, J=7), 6.74 (2H, d, J=9), 7.06 (2H, d, J=9), 7.12 (5H, s).

Method D——5-[4-[1-Methylcyclohexylmethoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of 3-bromo-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionitrile (2.5 g), thiourea (0.86 g) and sulfolane (20 ml) was stirred at 110°C for 2 h, then 2*N* HCl (20 ml) was added thereto. The mixture was refluxed for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave 49 (2.6 g, 98.0%), mp 130—131°C (from 85% EtOH). This sample was identical with an authentic sample of 49

SA61

prepared by method A.

The starting compounds used for this method were prepared as follows.

3-Bromo-4-[4-(3-methylcyclohexylmethoxy)phenyl]propionitrile: A mixture of 4-(3-methylcyclohexylmethoxy)nitrobenzene (8.0 g), 10% Pd/C (2.5 g) and MeOH (80 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated. The residual oil was dissolved in acetone (40 ml). To this stirred and ice-cooled solution, 47% HBr (72.5 g) and a solution of $NaNO_2$ (3.23 g) in H_2O (4 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min, then acrylonitrile (7.6 g) was added thereto and the temperature was raised to 35°. Cu_2O (0.5 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (80 g) using Et_2O–benzene (1: 10, v/v) as an eluent to give a pure oil (3.9 g, 48.1%). IR ν_{max}^{film} cm^{-1}: 2250. NMR δ: 1.02 (3H, d, 1.43 (10H, br sh), 3.25 (2H, d, J=7), 3.69 (2H, s), 4.37 (1H, t, J=7), 6.78 (2H, d, J=9), 7.10 (2H, d, J=9).

The following compound was similarly prepared.

3-Bromo-3-(4-cyclohexylmethoxyphenyl)propionitrile: Oil. Yield 43.8%. IR ν_{max}^{film} cm^{-1}: 2250. NMR δ: 1.2–2.2 (10H, br s), 3.15 (2H, d, J=7), 4.30 (1H, m), 4.32 (2H, t, J=7), 6.84 (2H, d, J=9), 7.14 (2H, d, J=9).

Method E——5-(4-Geranyloxybenzyl)thiazolidine-2,4-dione (41) and 3-Geranyl-5-(4-hydroxybenzyl)thiazolidine-2,4-dione (X, A=geranyl): A mixture of 57 (3.77 g, 50% NaH in oil (0.48 g) and DMSO (10 ml) was stirred at room temperature for 15 min and a solution of geranyl bromide (2.68 g) in DMSO (5 ml) was added thereto. The mixture was stirred at room temperature for 20 min, poured into H_2O, acidified with 2 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (80 g) with cyclohexane–AcOEt (4: 1, v/v). The first part of the eluate gave X (A=geranyl) (0.46 g, 35.0%), mp 85—86°C (from cyclohexane). IR ν_{max}^{Nujol} cm^{-1}: 3400—3500, 1760, 1660. NMR δ: 1.63 (3H, s), 1.68 (3H, s), 1.73 (3H, s), 2.0 (4H, m), 3.09 (1H, q, J=14 and 9), 3.42 (1H, q, J=14 and 4), 4.19 (2H, d, J=7), 4.37 (1H, q, J=9 and 4), 5.03 (1H, m), 5.37 (1H, m), 6.72 (2H, d, J=9), 7.03 (2H, d, J=9). *Anal.* Calcd for $C_{19}H_{25}NO_4S$: C, 63.83; H, 7.05; N, 3.92. Found: C, 63.81; H, 7.01; N, 3.81. The following part of the eluate gave 41 (0.9 g, 50.9%), mp 55—56°C (from cyclohexane–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1760, 1660. NMR δ: 1.60 (3H, s), 1.67 (3H, s), 1.70 (3H, s), 2.1 (4H, m), 3.00 (1H, q, J=14 and 9), 3.43 (1H, q, J=14 and 4), 4.18 (1H, q, J=9 and 4), 4.61 (2H, d, J=7), 5.06 (1H, m), 5.28 (1H, t, J=7), 6.80 (2H, d, J=9), 7.10 (2H, d, J=9), 8.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{25}NO_4S$: C, 63.83; H, 7.05; N, 3.92. Found: C, 63.78; H, 6.81; N, 3.83.

The following compounds were similarly prepared.

5-(4-Phytyloxybenzyl)thiazolidine-2,4-dione (42): mp 51—53°C (from hexane). Yield 40.9%. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1760, 1710. NMR δ: 0.8—0.9 (12H, br d), 1.1—2.3 (34H, m), 3.07 (1H, q, J=14 and 9), 3.50 (1H, q, J=14 and 4), 4.44 (1H, q, J=9 and 4), 4.47 (2H, d, J=7), 5.43 (1H, t, J=7), 6.80 (2H, q, J=9), 7.11 (2H, d, J=9), 8.50 (1H, br s). *Anal.* Calcd for $C_{34}H_{55}NO_3S$: C, 71.91; H, 9.61; N, 2.79. Found: C, 72.10; H, 9.56; N, 2.60.

5-(4-Hydroxybenzyl)-3-phytylthiazolidine-2,4-dione (X, A=phytyl): Oil. Yield 21.9%. IR ν_{max}^{film} cm^{-1}: 3300—3200, 1740, 1670. NMR δ: 0.85—0.95 (12H, br s), 1.15—2.2 (34H, m), 3.10 (1H, q, J=14 and 9), 3.47 (1H, q, J=14 and 4), 4.50 (1H, q, J=9 and 4), 4.45 (2H, d, J=7), 5.46 (1H, t, J=7), 6.81 (2H, d, J=9), 7.15 (2H, d, J=9).

Method F——5-[4-(3-Pyrrolidinylmethoxy)benzyl]thiazolidine-2,4-dione Hydrochloride (84·HCl): A mixture of methyl 3-[4-(1-benzyl-3-pyrrolidinylmethoxy)phenyl]-2-chloropropionate (5.4 g), thiourea (1.8 g) and BuOH (40 ml) was stirred at 110°C for 13 h and concentrated in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in AcOH (40 ml) and conc. HCl (40 ml). The mixture was refluxed for 33 h, cooled, diluted with H_2O and extracted with AcOEt. The aqueous layer was concentrated in vacuo and EtOH (30 ml)–MeOH (5 ml) was added to the residue. The insoluble solid was filtered off and the filtrate was concentrated to leave a crystalline residue. Recrystallization from EtOH gave colorless prisms (1.9 g, 32.3%), mp 163—164°C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2700—2600, 1740, 1690. NMR (d$_6$-DMSO) δ: 1.7—2.2 (4H, m), 3.3—4.0 (9H, m), 4.12 (2H, d, J=6), 6.93 (1H, q, J=9 and 4), 6.99 (2H, d, J=9), 7.18 (2H, d, J=9), 10.2 (2H, br). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$·HCl: C, 53.96; H, 5.69; N, 8.37. Found: C, 53.66; H, 5.86; N, 7.72.

5-(4-Aminobenzyl)thiazolidine-2,4-dione (74): A mixture of 5-(4-nitrobenzyl)thiazolidine-2,4-dione (10.0 g), 10% Pd/C (10.0 g) and MeOH (250 ml)–AcOEt (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo to give crystals of 74 (7.8 g, 88.6%). Recrystallization from MeOH gave light yellow prisms, mp 183—185°C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3200, 3060 (br), 1755, 1690. NMR (d$_6$-DMSO) δ: 2.96 (1H, q, J=14 and 9), 3.25 (1H, q, J=14 and 4), 4.73 (1H, q, J=9 and 4), 6.48 (2H, d, J=9), 6.88 (2H, d, J=9), 7.5—9.0 (3H, br). *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.08; H, 4.48; N, 12.75.

The starting material used for this method was prepared as follows.

Ethyl 3-Chloro-3-(4-nitrophenyl)propionate: Conc. HCl (25 ml) and a solution of $NaNO_2$ (1.8 g) in H_2O (15 ml) were added dropwise to a stirred and ice-cooled solution of *p*-nitroaniline (13.8 g) in acetone (150 ml) below 5°C. The whole was stirred at 5°C for 30 min, then ethyl acrylate (30 g) was added thereto and the

temperature was raised to 10°C. Et_2O (0.1 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo, diluted with H_2O and extracted with Et_2O. The usual work up gave an oily residue, which was purified by column chromatography on silica gel (140 g) using Et_2O–benzene (1: 10, v/v) as an eluent to give the title compound as an oil (16.5 g, 64.0%). IR ν_{max}^{film} cm^{-1}: 1735, 1510, 1345. NMR δ: 1.23 (3H, t, J=7), 3.28 (1H, q, J=14 and 7), 3.95 (3H, q, J=14 and 7), 4.15 (2H, q, J=7), 4.60 (1H, q, J=7), 7.36 (2H, d, J=9), 8.07 (2H, d, J=9).

5-[4-(Nitrobenzyl)thiazolidine-2,4-dione: A mixture of ethyl 2-chloro-3-[4-nitrophenyl]propionate (13.0 g), thiourea (7.6 g) and methanol (120 ml) was stirred at 130°C for 5 h and 2 N HCl (80 ml) was added thereto. The mixture was stirred at 100°C for 15 h, cooled and diluted with H_2O to give crystals. Recrystallization from MeOH gave colorless rods (9.0 g, 71.4%), mp 185—187°C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1750, 1695, 1345. NMR (d_6-DMSO) δ: 3.23 (1H, q, J=14 and 9), 3.87 (1H, q, J=14 and 4), 4.85 (1H, q, J=9 and 4), 7.45 (2H, d, J=9), 8.05 (2H, d, J=9), 11.9 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_2O_5S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.69; H, 3.31; N, 11.30.

5-[4-(p-Toluenesulfonylamino)benzyl]thiazolidine-2,4-dione (76): Reaction of 74 (4.0 g) and *p*-toluenesulfonyl chloride (3.5 g) gave the title compound (5.6 g, 96.6%), mp 224—225°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1740, 1690. NMR (d_6-DMSO) δ: 2.33 (3H, s), 3.07 (1H, q, J=14 and 9), 3.28 (1H, q, J=14 and 4), 4.79 (1H, q, J=9 and 4), 7.07 (4H, s), 7.32 (2H, d, J=9), 7.62 (2H, d, J=9), 10.13 (1H, s), 11.9 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_2O_5S_2$: C, 54.28; H, 4.29; N, 7.44. Found: C, 54.18; H, 4.38; N, 7.32.

5-(4-Propionylaminobenzyl)thiazolidine-2,4-dione (76): Reaction of 74 (2.2 g) and propionyl chloride (1.0 ml) gave the title compound (1.56 g, 66.8%), mp 140—141°C (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1750, 1690, 1655. NMR (d_6-DMSO) δ: 1.10 (3H, t, J=7), 2.39 (2H, q, J=7), 3.00 (1H, q, J=14 and 9), 3.38 (1H, q, J=14 and 4), 4.83 (1H, q, J=9 and 4), 7.33 (2H, d, J=9), 7.85 (2H, d, J=9). *Anal.* Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.79; H, 5.32; N, 9.83.

5-[4-Nicotinylaminobenzyl]thiazolidine-2,4-dione (77): Reaction of 74 (2.2 g) and nicotinoyl chloride [prepared from sodium nicotinate (1.74 g) and phosphorus oxytrichloride (0.97 g) according to the method of Russels *et al.*[6]] gave the title compound (1.0 g, 30.0%), mp 271—273°C (from DMF–H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3360, 1740, 1690, 1670. NMR (d_6-DMSO) δ: 3.06 (1H, q, J=14 and 9), 3.38 (1H, q, J=14 and 4), 4.88 (1H, q, J=9 and 5), 7.37 (2H, d, J=9), 7.4—7.7 (1H, m), 7.76 (2H, d, J=9), 8.33 (1H, d, J=7), 8.8 (1H, m), 9.1 (1H, m), 10.08 (1H, br d), 11.9 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}N_3O_3S$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.39; H, 4.01; N, 12.94.

5-[4-(3-Aminopropionylamino)benzyl]thiazolidine-2,4-dione Hydrobromide (78·HBr): A mixture of 5-[4-(3-benzyloxycarbonylaminopropionylamino)benzyl]thiazolidine-2,4-dione (1.9 g) and 25% HBr in AcOH (v/v, 20 ml) was stirred at room temperature for 30 min and diluted with Et_2O (100 ml). The crystalline precipitate was filtered off and recrystallized from MeOH to give 78·HBr (1.02 g, 41.6%), mp 242—243°C. IR ν_{max}^{Nujol} cm^{-1}: 2800, 2700—2300, 1750, 1690, 1640. NMR (d_6-DMSO) δ: 2.73 (2H, t, J=7), 2.9—3.5 (4H, m), 4.83 (1H, q, J=7 and 4), 7.18 (2H, d, J=9), 7.56 (2H, d, J=9), 7.9 (3H, br s), 10.17 (1H, s). *Anal.* Calcd for $C_{19}H_{19}N_3O_4S$·HBr: C, 41.72; H, 4.31; N, 11.53. Found: C, 41.36; H, 4.33; N, 11.10.

The starting material used for this method was prepared as follows.

5-[4-[3-Benzyloxycarbonylaminopropionylamino]benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of *N*-benzyloxycarbonyl-β-alanine (1.3 g). The mixture was stirred with ice-cooling for 15 min, and a solution of 74 (2.32 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, diluted with 2 N HCl (50 ml) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated to leave an oil, which was treated with Et_2O to give the title compound (3.1 g, 73.8%) as a powder. Crystallization from EtOH–Et_2O gave colorless prisms, mp 189—191°C. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1750, 1730, 1680. NMR (d_6-DMSO) δ: 2.4—2.7 (2H, m), 3.3—3.6 (4H, m), 4.89 (1H, q, J=8 and 5), 5.03 (2H, s), 7.1—7.6 (9H, m), 7.8 (1H, br d), 8.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{29}H_{29}N_3O_6S$: C, 59.89; H, 4.84; N, 9.82. Found: C, 59.88; H, 4.96; N, 9.66.

5-[4-[5-Aminobenzoylamino]benzyl]thiazolidine-2,4-dione (79): A mixture of 5-[4-[5-tert-butoxycarbonylaminobenzoylamino]benzyl]thiazolidine-2,4-dione (1.6 g) and 25% HBr in AcOH (v/v, 20 ml) was stirred at room temperature for 30 min then concentrated. The residue was charged on a column packed with Amberlite IRC-400 (AcO^-) (25 ml) and eluted with 20% MeOH (v/v). The solvent was evaporated off to give 79 as crystals (0.76 g, 47.9%), mp 216—218°C (from DMF–Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3300, 3250, 1670. NMR (d_6-DMSO) δ: 1.1—1.9 (6H, m), 2.5—3.4 (4H, m), 4.77 (1H, m), 7.1—7.7 (11H, m), 7.9 (2H, m), 9.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_4O_4S$: C, 56.39; H, 4.30; N, 12.31. Found: C, 56.50; H, 4.45; N, 12.59.

The starting material used for this method was prepared as follows.

5-[4-[5-tert-Butoxycarbonylaminobenzoylamino]benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of 5-*tert*-butoxycarbonylaminobenzoic acid (2.15 g) in CH_2Cl_2 (10 ml). The mixture was stirred with ice-cooling for 10 min and a solution of 74 (2.2 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at −10°C for 30 min and at room temperature for 1 h, concentrated *in vacuo*, neutralized

SA63

with 10% (w/w) citric acid aq. solution and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave the title compound as a crude oil (4.0 g, quant.). IR ν_{max}^{neat} cm^{-1}: 3050, 3130, 1760, 1710, 1600. NMR (d_6-DMSO) δ: 1.2—1.7 (6H, m), 1.36 (9H, s), 2.1—2.5 (2H, m), 2.8—3.5 (4H, m), 4.00 (1H, q, J=8 and 5), 6.58 (1H, br d), 7.1—7.6 (4H, m), 9.75 (1H, br s), 11.95 (1H, br s). The crude oil was used for the subsequent reaction without purification.

5-(4-Ethoxycarbonylmethyleneaminobenzoylamino-4-hexenyl)thiazolidine-2,4-dione (93): A solution of ethoxycarbonylmethylidenetriphenylphosphorane (2.65 g) in THF (5 ml) was added dropwise to a stirred and ice-cooled solution of 74 (1.1 g) in THF (10 ml). The mixture was stirred at 0°C for 1 h and at room temperature for 10 h, poured into H_2O and extracted with AcOEt. The usual work-up gave crystals of 93 (0.58 g, 38.7%). Recrystallization from EtOH gave colorless prisms, mp 161—162°C. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3170, 1750, 1690. NMR δ: 1.28 (3H, t, J=7), 3.91 (1H, q, J=14 and 8), 3.43 (1H, q, J=14 and 4), 3.97 (2H, d, J=5), 4.18 (2H, q, J=7), 6.52 (1H, q, J=8 and 1), 6.87 (1H, q, J=5), 7.08 (2H, d, J=9), 7.36 (2H, d, J=9), 8.5 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{16}H_{17}N_3O_5S$: C, 51.21; H, 4.83; N, 11.96. Found: C, 51.11; H, 4.83; N, 11.77.

5-(4-Phenethylaminobenzoyl)thiazolidine-2,4-dione Hydrochloride (80·HCl): A mixture of 5-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzoyl]thiazolidine-2,4-dione (3.5 g), conc. H_2SO_4 (15 ml) and AcOH (15 ml) was stirred at 100°C for 1 h, cooled, neutralized with sat. aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was treated with a solution of HCl in Et_2O (3.54 mmol/g, 10 ml) to give crystals of 80·HCl (1.7 g, 63.0%). Recrystallization from acetone gave colorless needles, mp 156—157°C. IR ν_{max}^{Nujol} cm^{-1}: 3360—2200, 1730, 1690. NMR (d_6-DMSO) δ: 2.8—3.6 (6H, m), 4.38 (1H, q, J=8 and 4), 7.25 (2H, s), 7.33 (5H, d, J=9), 7.40 (2H, d, J=9), 8.1—8.7 (2H, br), 12.0 (1H, br). *Anal.* Calcd for $C_{18}H_{18}N_2O_3S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.43; H, 5.36; N, 7.66.

The starting material used for this method was prepared as follows.

4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline: A mixture of 4-(*p*-toluenesulfonylamino)aniline[9] (13.1 g), 60% NaH in oil (2.64 g) and DMF (150 ml) was stirred at room temperature for 30 min, then phenethyl bromide (11.1 g) was added thereto. The mixture was stirred at 70°C for 2 h, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil, which was chromatographed on silica gel (300 g). Elution with $CHCl_3$ gave crystals of the title compound (13.6 g, 74.6%), mp 105—106°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3450, 3370, 1335, 1155. NMR δ: 2.43 (3H, s), 2.85 (2H, t, J=7), 3.7—4.0 (4H, m), 6.43 (2H, d, J=9), 6.90 (2H, d, J=9), 7.2—7.8 (9H, m). *Anal.* Calcd for $C_{23}H_{24}N_2O_2S$: C, 68.32; H, 6.46; N, 7.85. Found: C, 69.04; H, 6.60; N, 7.76.

Methyl 3-Chloro-3-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl]propionate: $CuCl_2$·2H$_2$O (3.7 ml) and a solution of $NaHSO_3$ (2.64 g) in H_2O (10 ml) were added dropwise to a stirred and ice-cooled solution of 4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline (13.7 g) in acetone (150 ml)–MeOH (100 ml) below 5°C. The mixture was stirred at 5°C for 15 min and methyl acrylate (15.0 g) was added thereto. The temperature was raised to 35°C and Cu_2O (0.5 g) was added portionwise to the mixture with vigorous stirring. After N_2 gas evolution had ceased, the mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (200 g) with cyclohexane–AcOEt (3 : 1, v/v) to give a pure oil (8.5 g, 99.8%). IR ν_{max}^{neat} cm^{-1}: 1750, 1340, 1155. NMR δ: 2.43 (3H, s), 2.8—4.1 (6H, m), 4.58 (1H, q, J=9 and 4), 7.0—7.7 (13H, m), 9.5 (1H, br s).

5-[4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzyl]thiazolidine-2,4-dione: A mixture of 3-chloro-3-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl]propionate (9.5 g), thiourea (3.1 g) and ethylene glycol (100 ml) was stirred at 130°C for 16 h, then 1*N* HCl (40 ml) was added. The mixture was refluxed for 5 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g) with cyclohexane–AcOEt (3 : 1, v/v) to give the title compound as an oil (8.5 g, 67.3%). IR ν_{max}^{neat} cm^{-1}: 3310, 1765, 1705, 1340, 1155. NMR δ: 2.40 (3H, s), 2.8—4.1 (6H, m), 4.58 (1H, q, J=9 and 4), 7.0—7.7 (13H, m), 9.5 (1H, br s).

5-[4-(5-Chloro-2-methoxybenzoylamino)benzyl]thiazolidine-2,4-dione (82): A mixture of 5-chloro-2-methoxybenzoic acid (1.61 g), thionyl chloride (1.73 ml) and C_6H_6 (20 ml) was refluxed for 1 h, then concentrated *in vacuo* to leave an oil. The oil was dissolved in DMF (10 ml) and the solution was added to a solution of 74 (1.9 g) in DMF (10 ml). The mixture was stirred at room temperature for 30 min, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals of 82 (1.55 g, 48.6%). Recrystallization from MeOH gave colorless prisms, mp 231 – 232°C. IR ν_{max}^{Nujol} cm^{-1}: 3220, 3100, 1740, 1685, 1640. NMR (d_6-DMSO) δ: 3.03 (1H, q, J=14 and 8), 3.40 (1H, q, J=14 and 4), 4.65 (1H, q, J=8 and 4), 7.0—7.8 (7H, m), 10.26 (1H, s), 12.1 (1H, br s). *Anal.* Calcd for $C_{18}H_{15}ClN_2O_5S$: C, 56.22; H, 3.97; N, 7.12. Found: C, 56.30; H, 3.81; N, 7.26.

5-[4-[3-(Pyrrolidinyl)benzoyl]thiazolidine-2,4-dione Hemihydrate (83·1/2H$_2$O): A mixture of 74 (3.84 g), bis(3-chloroethyl)amine hydrochloride (3.8 g) and MeOH (15 ml) was refluxed for 25 h. After removal of the solvent, the residue was partitioned between $CHCl_3$ and sat. aq. $NaHCO_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel (100 g) using $CHCl_3$–MeOH (9 : 1, v/v) as an eluent to give crystals of 83. Recrystallization from MeOH gave colorless prisms (0.23 g, 5.3%), mp 231—233°C. IR ν_{max}^{Nujol} cm^{-1}: 1680. NMR (d_6-DMSO) δ: 2.7—3.4

SA64

[1H], m], 4.23 [1F, q, J = 9 and 6], 6.82 [2F, d, J = 9], 7.10 [2H, d, J = 9], 9.0 [1H, br], 12.0 [1H, br]). *Anal.* Calcd for $C_{20}H_{19}N_3O_4S \cdot 1/2H_2O$: C, 58.50; H, 5.06; N, 12.98. Found: C, 58.31; H, 5.39; N, 11.92.

Diethyl 4-(4-Chlorophenoxy)butylmalonate: Diethyl malonate (7.7 g) and a solution of 4-(4-chlorophenoxy)butyl bromide[10] (11.5 g) in EtOH (80 ml) were added dropwise to a stirred solution of Na (1.1 g) in EtOH (80 ml) at room temperature. The mixture was refluxed for 3 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue which was chromatographed on silica gel (150 g). Elution with Et_2O–hexane (1:2, v/v) gave a pure oil (11.2 g, 76.7%). IR ν_{max}^{film} cm^{-1}: 1745, 1725. NMR δ: 1.22 [6H, t, J = 7], 1.5—2.2 [4H, m], 3.33 [1H, t, J = 7], 3.80 [2H, t, J = 5], 4.15 [4H, q, J ~7], 6.63 [2H, d, J = 8], 7.10 [2H, d, J = 8].

Diethyl α-Chloro-α-[4-(4-chlorophenoxy)butyl]malonate: A mixture of diethyl 4-(4-chlorophenoxy)-butylmalonate (10.0 g) and sulfuryl chloride (5 g) was heated at 70°C for 3 h, then concentrated. The residue was dissolved in Et_2O (500 ml). The solution was successively washed with H_2O, sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and concentrated to give crystals (9.9 g, 91.7%). Recrystallization from hexane gave colorless needs, mp 31—32°C. IR ν_{max}^{KBr} cm^{-1}: 1740. NMR δ: 1.27 [6H, t, J = 7], 1.6—2.6 [4H, m], 3.39 [1H, t, J = 7], 3.91 [2H, t, J = 6], 4.30 [4H, q, J ~7], 6.70 [2H, d, J = 9], 7.22 [2H, d, J = 9]. *Anal.* Calcd for $C_{19}H_{26}Cl_2O_5$: C, 54.12; H, 6.22. Found: C, 54.20; H, 6.08.

3-Chloro-4-[4-(4-hydroxyphenoxy)butyramido] Acid: A solution of diethyl α-chloro-α-[4-(4-chlorophenoxy)-butyl]-malonate (9.77 g), AcOH (15 ml) and 6 N HCl (15 ml) was refluxed for 20 h, cooled, diluted with H_2O and extracted with CH_2Cl_2. The usual work-up gave 6.6 g crystals (5.0 g, 66.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 59—59°C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1745, 1690. NMR δ: 1.8—2.6 [4H, m], 3.75 [2H, t, J = 7], 4.50 [1H, t, J = 7], 6.75 [2H, d, J = 8], 7.35 [2H, d, J = 8], 8.70 [1H, br s]. *Anal.* Calcd for $C_{12}H_{14}ClNO_4S$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.11; H, 4.82; N, 4.80.

3-Hydroxy-3-(4-phenethyloxybenzyl)succinic Acid: CH_2N_2 (13.5 g) was added to a stirred and ice-cooled mixture of 4-phenethyloxybenzaldehyde[11] (21.2 g), LiCl (4.5 g), KOH (13.2 g), H_2O (64 ml) and dioxane (60 ml). The mixture was stirred at 5°C for 15 h, then at 85°C for 25 h, acidified with 9 N HCl and extracted with Et_2O. The usual work-up gave crystals of the title compound (8.9 g, 79.1%). Recrystallization from AcOEt–hexane gave colorless needles, mp 120—122°C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1745, 1715. NMR δ: 2.97 [2H, t, J = 7], 4.0 [1H, br s], 4.30 [2H, t, J = 7], 6.10 [1H, s], 6.87 [2H, d, J = 8], 7.20 [4H, s], 7.30 [2H, d, J = 8]. *Anal.* Calcd for $C_{20}H_{22}O_6$: C, 70.17; H, 6.48. Found: C, 70.74; H, 6.64.

Methyl 2-Hydroxy-3-(4-phenethyloxyphenyl)acetate: Reaction of 3-hydroxy-3-(4-phenethyloxybenzyl)-succinic acid (3.7 g) and a solution of CH_2N_2 in Et_2O gave the title compound as an oil (3.0 g, quant.). IR ν_{max}^{film} cm^{-1}: 3500, 1740. NMR δ: 3.10 [2H, t, J = 7], 3.63 [1H, d, J = 6], 3.73 [3H, s], 4.30 [2H, t, J = 7], 5.16 [1H, d, J = 3], 6.9—7.4 [9H, m].

Methyl 2-Chloro-3-(4-phenethyloxyphenyl)-acetate (XI): Thionyl chloride (0.22 ml) and pyridine (0.32 ml) were added to a solution of methyl 3-hydroxy-3-(4-phenethyloxyphenyl)-acetate (0.8 g) in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 1 h and at 30°C for 30 min, then concentrated in vacuo. The residue was diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue, which was chromatographed on silica gel (20 g). Elution with cyclohexane–AcOEt (5:1, v/v) gave XI as an oil (0.36 g, 66.0%). IR ν_{max}^{film} cm^{-1}: 1755. NMR δ: 3.08 [2H, t, J = 6], 3.75 [3H, s], 4.18 [2H, t, J = 6], 5.30 [1H, s], 6.7—7.5 [9H, m].

3-(4-Phenethyloxyphenyl)-thiazolidine-2,4-dione (XII): A mixture of XI (0.66 g), thiourea (0.38 g) and sulfolane (2 ml) was stirred at 110°C for 4 h, then 2 N HCl (3 ml) was added thereto. The mixture was stirred at 100°C for 15 h, diluted with H_2O and extracted with Et_2O. The usual work up gave crystals of XII (0.22 g, 55.0%). Recrystallization from EtOH gave colorless prisms, mp 123—125°C. IR ν_{max}^{KBr} cm^{-1}: 3180, 1765, 1725, 1695. NMR δ: 3.10 [2H, t, J = 8], 4.30 [2H, t, J = 8], 5.33 [1H, s], 6.97 [2H, d, J = 9], 7.31 [2H, d, J = 9], 7.39 [5H, s], 9.0 [1H, br s]. *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 66.10; H, 4.81; N, 4.47. Found: C, 65.98; H, 4.89; N, 4.80.

Ethyl 2-Chloro-3-(4-pivaloyloxyphenyl)propionate: A solution of ethyl 3-chloroacetoacetate[12] (1.6 g) in DMF (10 ml) was treated with 60% NaH in oil (0.44 g) and the mixture was stirred at room temperature for 30 min. 4-Pivaloyloxybenzyl bromide[13] (3.1 g) was added to the mixture. The whole was stirred at 70°C for 2 h, poured into ice-H_2O, acidified with 1 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in EtOH (30 ml), and $Fe(OH)_3$–IH_2O (1.3 g) was added to the stirred and ice-cooled solution. After being stirred for 30 min, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (40 g) using cyclohexane–ice Et_2O (5:1, v/v) as an eluent to give the title compound (3.18 g, 48.8%) as a pure oil. IR ν_{max}^{film} cm^{-1}: 1760, 1670. NMR

SA65

δ: 0.23 (3H, t, J=7), 1.23 (9H, s), 4.12 (1H, q, J=14 and 3), 3.60 (1H, q, J=14 and 7), 4.13 (2H, q, J=7), 4.35 (1H, t, J=7), 7.20 (5H, d, J=2), 7.65 (5H, d, J=9).

Ethyl 2-Chloro-3-(3,4-dimethoxyphenyl)propionate: Reaction of 3,4-dimethoxybenzyl chloride[11] (22.5 g) and 2-chloroacetoacetate[12] (19.2 g) gave the title compound as an oil (13.7 g, 38.9%). IR: ν_{max}^{liq} cm^{-1}: 1740. NMR δ: 1.21 (3H, t, J=7), 3.60 (1H, q, J=14 and 7), 3.39 (2H, q, J=14 and 7), 3.73 (6H, s), 4.15 (2H, q, J=7), 4.27 (1H, t, J=7), 6.68 (2H, s).

2-Chloro-3-(3,4,5-trimethoxyphenyl)propionic Acid: The condensation of 2-chloroacetoacetate[12] (4.33 g) with 3,4,5-trimethoxybenzyl chloride (5.5 g) followed by treatment with 2 N KOH (30 ml) gave the title compound as crystals (6.5 g, 68.9%), mp 98—99°C (from AcOEt–hexane). IR: ν_{max}^{Nujol} cm^{-1}: 1735. NMR δ: 1.37 (3H, t, J=7), 3.60 (3H, t, J=7), 3.42 (2H, t, J=7), 3.68 (3H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 3.8—4.4 (6H, m), 4.42 (1H, t, J=7), 6.63 (1H, q), 6.73 (1H, s), 10.56 (1H, s). *Anal.* Calcd for $C_{12}H_{15}ClO_5$: C, 50.97; H, 6.48. Found: C, 50.91; H, 6.70.

Acknowledgment The authors wish to thank Drs. M. Hashimoto and M. Iwakubo for constant support throughout this work.

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61hWtak1

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants.

New York, N Y.
January 17, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

61hWtak1

APPEARANCES

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JOHN S. GOETZ

A. Right.
Q. Right there in the first sentence of the second full paragraph, page 347, second column, right?
A. Right.
Q. It says, "In the rodent, 25 percent of the total brown fat is" – excuse me. I'm going to mispronounce this word.
A. Perirenal.
Q. What is that?
A. Around the kidney.
Q. It says rodent, right?
A. Correct.
Q. And it cites reference 20?
A. Yes.
Q. Did you read reference 20?
A. I did not.
Q. Did you read the title to reference 20?
A. I don't believe I did.
Q. It's right on the next page there.
A. I've read it.
Q. Refers to rats, doesn't it?

A. Sure, yes.
Q. All right. And the authors used rodents in another part of this document, in that same paragraph, the last sentence. See that?
A. Yes, I see that.
Q. They say rodents again, right?
A. Yes.
Q. They cite two references this time. Did you read those references?
A. I did not.
Q. Did you look at the title of those references?
A. I don't believe so.
Q. Those references refer to rats, don't they?
A. Yes.
Q. So when the authors say rodents, they say rats, they mean rats?
A. Not necessarily.
Q. Not necessarily?
A. No.

Q. But they cite the references with rats, discussing rats?
A. But rodents is a general term, and rat's just one animal that's in a rodent.
Q. Now, the article talks about brown fat?
A. Yes, it does.
Q. And thermogenesis?

A. Yes.
Q. Thermogenesis is heat generation, isn't that true?
A. Yes, it is.
Q. And the article talks about cold-induced thermogenesis?
A. Yes.
Q. What is that?
A. I have to see where they talk about it. Do you have that outlined?
Q. Yeah. I believe they talk about it at least in the second column, page 343.
A. That's, it says, "In small mammals, brown fat is a major site of nonsugar and thermogenesis-producing heat in cold exposure," so that's cold-induced thermogenesis.
Q. They also talk about dietary-induced thermogenesis, right?
A. Yes.
Q. What's that?
A. That's dissipating excess calories when overfed.
Q. That's when they eat too much, right?
A. Yes.
Q. You get sweaty?
A. Some people do.
Q. Hot under the collar?
A. I don't know.
Q. Face gets flushed, maybe?
A. Possible.

Q. And heat generation in that manner can play a role in the regulation of body weight, right?
A. Yes.
Q. That makes sense, doesn't it?

A. You're talking about thermogenesis?
Q. Yes. The body generates heat and weight is lost, right?
A. And weight loss?
Q. And weight is lost, right?
A. Yes.
Q. In 1985, according to this article, there was speculation that brown fat in humans may contribute to thermogenesis. That's what it says, right?
A. That's what it says.
Q. So brown fat might be related to the regulation of body weight then, right?
A. Possible, but it was unknown.
Q. All right. Let's turn to page 347. And look at the paragraphs bridging columns 1 and 2. All right? It's actually one paragraph. Sorry. See that paragraph?
A. Which one? I'm -- which paragraph, in column 1?
Q. There's actually a paragraph that's both on column 1 and in column 2.
A. Starts on the bottom of column 1?
Q. Right.
A. Okay.

Q. See that paragraph?
A. Sure.
Q. So some believe that thermogenesis defect may lead to obesity, right?
MR. CONLIN: I object, your Honor.
THE COURT: Sustained.
MR. GOETZ: Okay.
Q. The last sentence in that paragraph talks about speculation. Do you see that?
A. Yes.
Q. What do you understand that to mean?
A. Well, what they're talking about here is there's debate concerning the dietary-induced faculty of thermogenesis in man. So this article, this article basically is studying the thermogenesis, and they want to compare it and see if it's, thermogenesis in man is similar to that that is known in animals. And then they go on to state that there's some doubt if it's actual existence where it suggests there can be

defective in obese man, and some speculated the defect may have been involved brown fat.

So they're talking about a defect in obese man on the effect of brown fat. So --

Q. Sorry.

A. And that it might be somewhat similar to that you see in some genetic strains of rodents.

Q. So they're comparing brown fat in man to brown fat in rodents, right?

A. Well, yes. What they're trying to do is, what they're saying here is we don't know for sure what goes on with the brown fat, is the -- what do I want to say? Does brown fat, is the activity of brown fat in humans correlative to brown fat in rodents, that's what their question is.

Q. That's the speculation they're looking into there in the last sentence, right?

A. That's, that's the way I read this, yes.

Q. And the authors disagreed with that speculation, didn't they?

A. Well, what the authors found was that they didn't find the correlation, and this study, the type of study they did, where they were looking at the mitochondria, and uncoupling of protein in mitochondria which was shown in rodents, they didn't find that in man at, near the activity.

Q. The authors found the brown fat cannot be involved in any genetic defect in humans, right?

A. I don't see, I don't think they conclude that.

Q. Well, you see the last sentence I have up here on the screen, in the second full paragraph on page 347, second column, right?

A. Okay. Where are we at here? I have to find out where we're at.

Q. Sure.

A. Okay. Now, would you ask me the question, please.

Q. The sentence says contrasts, doesn't it?

A. Yes.
Q. Over a hundred?
A. I would suspect.
Q. And some of those -- oh, withdrawn.
Over a period of 28 years or so, is that right?
A. Yes.
Q. And some of those presentations were on papers that you wrote, right?

A. Yes.
Q. You've never given a presentation on the prospective pharmaceutical compound, have you?
A. A presentation on -- oh, boy.
MR. CONLIN: I object. I don't understand the term.
THE COURT: Sustained.
BY MR. GOETZ:
Q. Do you know what a lead compound is?
A. A lead compound is, in this case, would be a compound that they were pursuing to be an antidiabetic drug.
Q. Have you ever given a presentation on how to select a lead compound?
A. I have not.
Q. Have you ever written a paper on that?
A. I have not.
Q. But you have written a few papers, right?
A. Yes.
Q. Over a hundred?
A. Yes.
Q. And some of these published -- were they published papers?
A. Yes.
Q. And some of these published papers were based on the results of toxicological tests, right?
A. Yes.
Q. And you would typically oversee these studies if you're

going to write about them, is that how it works?
A. That's not necessarily true.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
----------x
TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.
----------x
TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants.
----------x

New York, N.Y.
January 24, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

APPEARANCES

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JEFFREY A. HOVDEN
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I read review articles, for instance, in medicinal chemistry.
Q. Sir, do you recall at your deposition being asked these questions and giving these answers:
"Q. What medicinal chemistry books do you have on your shelf today?
"A. From back then or --
"Q. No, no, any time. Any time. If I walk into your office,

what medicinal chemistry texts do I see?
"A. You'll find a lot of journal stuff with review article type stuffs. I don't really have time to read texts out of my field. So that's what you would find, review articles."
Do you recall that, sir?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. I recall making that statement. And I, what I meant by that was serious reading. If you're asking would I have had a book -- Gilman, for instance, a famous book, in medicinal chemistry, I own Gilman, whether it's on my desk right now, on my bookcase right now. But what that would mean is I would very quickly browse Gilman. I think that's what I would do. But I would read a review article. But Gilman I would just browse.
Q. In response to asking what medicinal chemistry texts you had, you said you didn't have time to read texts out of your field. Are you referring to medicinal chemistry there?
A. Sure, but I have to explain. Read to me means sort of a serious, in-depth experience. Browse means you quickly try to get something, you know, very quickly and it's all a matter of time allocation. So browse, I would do. I certainly had Gilman. Whether I have it today, I'm not sure.
Q. So you're known primarily as a synthetic chemist, is that right?

A. That is true.
Q. Now, you do make some statements in your declaration regarding medicinal chemistry?

A. I do make such statements.
Q. You talked about drug discovery?
A. I did.
Q. Are you familiar with homologation and walking substituents around a ring as techniques in drug discovery?
A. I'm familiar with such language. It's not, it has to be put in a very sharp contextual setting, but I have heard this language used, certainly.
Q. What is a homolog?
A. Technically, a homolog is a substance that differs from its precursor by a CH2 unit.
Q. I see. And if it differs by two CH2 units, is that still a homolog?
A. It would be in the realm of homology. I think the technical -- you want the technical meaning or as the, as what would be used in bantering?
Q. I would like your, your understanding as a synthetic chemist of the meaning of that question.
A. In my judgment, as a synthetic or any chemist for that matter, homolog means the unit of commerce, so to speak, in an organic structure is CH2. So II differs from methyl by CH2. Methyl differs from ethyl by CH2. So an ethyl from propyl by

CH2. So the homolog, if you look at the difference between a precursor structure and its final structure, it would be a CH2. If you're asking if you made two such changes, you would probably be best describing it as a bis homolog or a twofold homolog.
Q. What is an analog?
A. Now, an analog is the more general term, which probably defies precise definition. That's kind of in the eyes of the beholder. It's a structure -- if I had to give you a little more clarification of that, it would be a structure provoked by some other structure. In other words, if you have structure A, it might provoke sort of intellectually the possibility of structure B.
Q. Now, what is homologation?
A. Well, now, the term homologation is, it's a term, I guess technically, in principle, it would be adding a CH2 group to an entity, somehow. Somehow in the system there would be added a

CH2 group.
Q. Well, is it a way of making small changes to try to optimize the balance of toxicity and potency in drug development?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. You're asking is that the primary purpose of homologation?
Q. Is homologation a way of making such small changes, to

optimize?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. Homologation is a way of making small changes. The purpose of doing the homologation would be very context driven. It may be a small change, it may be a very large change in consequence. Homologation may have profound changes. It may have small changes. But homologation, you're asking me as a chemist, and a scientist, homologation is the act of expanding a structure by a CH2 group, somewhere.
Q. Right. And that would be to optimize the --
A. That's something separate. That's something you may or may not have at your purpose for homologation.
Q. Sir, I'm going to ask you again about your deposition page 98, lines 15 to 22.
A. Do I have that here?
Q. Would you like to get a copy?
A. Yeah. What was the page number?
Q. Page 98. And the lines are 15 to 22 -- I'm sorry. 14 to 22.
A. Right.
Q. Now, were you asked these questions and did you give these answers:
"Q. Before you get to the homologation stage that you talked about, let's assume --

"A. Actually, I don't remember talking about that as a desirable way to go. I said one would make small changes to

optimize, but it may be homologation.
"Q. Homologation would be one way of making the small changes?
"A. In principle."
Do you see that.
A. I do.
MR. VIOLA: Objection.
THE COURT: Sustained. Stricken.
BY MR. HOVDEN:
Q. Do you agree, Doctor, that homologation is one way of making small changes to optimize the properties of a molecule?
A. Well --
MR. VIOLA: Objection.
A. I have trouble --
THE COURT: Overruled.
A. I have trouble understanding the question. Homologation is a straightforward term. It means to expand a structure by unit. That's what it means scientifically. Now, why one does that, that's some, that's not the only reason to do homologation. It's one of different reasons, a menu of reasons. So, I'm afraid you're getting me to, we're confusing, the sum of you and me are confusing motive with act. Act of homologation is to add a CH2 group. It's as simple as that. Now, why one does that? There could be a menu of reasons for

doing that. So I'd like to know exactly what the thrust of your question is.
Q. Let me ask you this question, Doctor. If one wants to optimize the properties of a molecule, is homologation one technique that can be used to accomplish that?
A. It's a very context -- is it one of many possibilities? It is one of many possibilities.
Q. And homologation is a pretty standard technique in medicinal chemistry, isn't that right?
A. I wouldn't concede that point. It's not a matter of my conceding; I don't see it that way. It's very much dependent on the context of the situation as to whether it's something that you would do.
Q. Well, is it your understanding, your understanding is medicinal chemistry is a science?
A. I do.

Q. And as such, you would expect it to have some principles, right?
A. Sure. There are guiding, there are, let's say, protocols that are followed.
Q. And techniques?
A. There are strategies and techniques.
Q. Textbooks and courses, right?
A. Certainly.
Q. And would you expect that in textbooks in the early 1980s,

that homologation would be taught as a technique?
A. Truth of the matter is, I don't remember it as being described as a technique. It is one of many acts that people might undertake in the hope of improving a structure. But is it something that every schoolboy would be taught, that's what you do, start homologizing, I don't think that's right. I don't think that's correct.
Q. My question, Doctor, is medicinal chemistry textbooks of the early '80s, would you expect homologation to be taught in those textbooks?
A. It would appear in there, but I would not expect it to be taught as sort of the way to go.
Q. Ring walking, Doctor, what is that?
A. Ring walking?
Q. Yeah.
A. Well, I take it it means, if you have a certain ring which you regard in your mind as a fixed matrix, which is not going to change, then, and you have a particular substituent on the ring, that term would imply perhaps the movement of that substituent somewhere in that ring.
Q. In the materials you reviewed for this case, did you see any examples of ring walking of substituents?
A. I remember that term or something very close to that term appearing in, for instance, the Mosberg report.
Q. And, in fact, in I think paragraph 129 of your declaration,

you admit that Takeda didn't invent the technique, is that

right?
A. I could tell you that without looking. They did not invent the technique --
Q. Okay.
A. -- of changing the position of substituents.
Q. That was another standard technique as of the early 1980s, is that right?
A. Standard and context that would require elaboration on my part. Was it out there? Yes. Was it practiced? Only in certain situations.
Q. Now, Doctor, when you reviewed the -- are you familiar with the Sohda article?
A. Yes.
Q. And that's PTX76, I believe.
THE COURT: Could you spell that?
MR. HOVDEN: S-O-H-D-A.
THE COURT: Oh.
MR. HOVDEN: Maybe it's my Midwestern accent.
THE COURT: Well, I'm a Midwesterner. I thought you said Selig.
MR. HOVDEN: Sorry, your Honor.
THE COURT: No. Thank you.
BY MR. HOVDEN:
Q. At one point, Doctor, you systematically went through the

ethyl and methyl substituents on the phenyl ring, is that right?
A. There were --
MR. VIOLA: Objection.
THE COURT: Sustained.
BY MR. HOVDEN:
Q. Doctor, at any point, did you review, in particular, the ethyl and methyl substituents on the phenyl ring in the Sohda article?
A. I certainly looked at them.
Q. Right.
A. Took note of them.
Q. And, in fact, what you're reviewing is reviewing the results of homologation and ring walking, is that right?
A. I look at many aspects in Sohda, including changes of whole

MR. BROWN: I believe that that will take care of most of the issues.

THE COURT: Okay.

MR. BROWN: One other matter, in order to expedite things. There are four Alphapharm trial exhibits that we intend to offer during the examination of these two witnesses. And I just discussed it with plaintiffs' counsel, and they have no objections.

THE COURT: And they are.

MR. BROWN: Alphapharm Trial Exhibit 224.

THE COURT: 224 is received.

(Defendant's Exhibit Alphapharm 224 received in evidence)

MR. BROWN: 217.

THE COURT: 217's received.

(Defendant's Exhibit Alphapharm 217 received in evidence)

MR. BROWN: 226.

THE COURT: 226 is received.

(Defendant's Exhibit Alphapharm 226 received in evidence)

MR. BROWN: And 219.

THE COURT: And when I said those numbers, I should have in each instance said Alphapharm. So it's Alphapharm 217, 219, 224, and 226 that are received.

(Defendant's Exhibit Alphapharm 219 received in evidence)

MR. MURPHY: Your Honor, there's one more, it's Alphapharm 233, which is also not objected to.

THE COURT: It's received.

(Defendant's Exhibit Alphapharm 233 received in evidence)

THE COURT: Dr. Colca.

GERARD COLCA,

called as a witness by the Plaintiffs,

having been duly sworn, testified as follows:

THE COURT: I believe you're being given a copy of your trial declaration which is Exhibit --

MR. VIOLA: 430.

THE COURT: Did you read that carefully before signing it?

THE WITNESS: Yes.

THE COURT: Do you swear to the truth of its contents?

THE WITNESS: Yes, I do.

THE COURT: Any objections?

430 is received.

(Plaintiffs' Exhibit 430 received in evidence)

MR. VIOLA: Your Honor, at this time we'd like to move in the associated Takeda trial exhibits, 107, 109, 111, 113, 115, and 359.

MR. DiLELLO: Your Honor, regarding 359, I'm going to be cross-examining Dr. Colca about that. And would I be permitted to reserve an objection? Depending what comes out of my examination, I may move to strike it.

THE COURT: That's fine. It will, all of these exhibits are received. Exhibit 359 is received subject to potentially being struck if there is an objection as we go along.

(Plaintiffs' Exhibits 107, 109, 111, 113, 115, and 359 received in evidence)

CROSS-EXAMINATION

BY MR. BROWN:

Q. Good afternoon, Dr. Colca.

A. Good afternoon.

Q. I'd like to start by focusing on paragraph 31 of your trial declaration that's in front of you. And in this paragraph, you mentioned four particular toxicities that you primarily focused on in the screening tests for a successor compound to ciglitazone. Is that correct?

A. I think so. Should I read it?

Q. Please, to yourself.

A. Okay. I recall now.

Q. And those four are eye lens, heart, liver, and red blood cells, correct?

A. That's correct.

Q. You don't mention weight gain as a toxicity measure that you've used in the screening, and I wanted to ask you, in the 1983-1984 time frame, weight gain in diabetic animals, in an animal model was not something that would warrant the Upjohn researchers off of studying a particular thiazolidinedione, is it?

A. They would not, that's correct.

Q. Isn't that because weight gain in diabetic animals in those tests is caused partly by the fact that without treatment, the animals are dumping a lot of calories in their urine and the drug you're testing fixes that?

A. That is correct.

Q. And the animal continues to eat as much as usual, but without dumping the calories in the urine, it predictably gains weight?

A. That's correct.

Q. And, in fact, Doctor, this phenomenon of weight gain in animal models was observed by Takeda and Upjohn in 1983 or 1984 with ciglitazone, correct?

A. Yes. It depends on the animal model, but in some animal models. I should say not everybody felt the same way. That's what I felt, is that the weight gain was part of the pharmacology.

Q. You also don't focus on something called brown fat or brown adipose tissue in the toxicities you used to screen. Why is

that?

A. I don't know why we should.

Q. Upjohn was never warned away from continuing the development of any of the thiazolidinediones because of brown fat or brown adipose tissue, was it?

A. I didn't consider it a problem, no.

Q. In fact, some people thought it was a positive, didn't they?

A. That's correct.

Q. Dr. Colca, in paragraph 42 of your trial declaration, you

detailed the methodology for a four-day test that Upjohn performed on KKA yellow mice for blood glucose and, blood glucose lowering and triglyceride lowering, and I'd like you to just review that paragraph and confirm for me that that's the case.
A. That's correct.
Q. And in here, you discuss Upjohn's standard protocol for these types of tests, is that correct?
A. Yes.
Q. You state, "We began by carefully matching a pool of animals by age, body weight, and nonfasting blood glucose." Is that correct?
A. That's correct.
Q. Why did you carefully match the animals by nonfasting blood glucose?

A. These animals have a range of glucose levels, and so if you were to pick a group without matching them, you might run the risk that one particular group would be lower than the other. And that will make it then harder to show differences. You could be so unlucky as to have animals with all the lowest glucose end up in the control group, for example.
Q. Why did you carefully match the animals by body weight?
A. Well, we're, we want to match the doses as well. And so, the closer they are in match to body weight, the doses are going to be more similar too.
Q. You would ultimately normalize the body weights, is that correct?
A. The results should do, but the amount of drug the animal gets will be dependent on the amount of food that he eats.
Q. Doctor, why did you carefully match the animals by age?
A. Well, generally, they were all about the same age in this particular case. You want to match the groups for all the parameters you could think of to be as close as possible.
Q. Why did you single out age here, or --
MR. VIOLA: Objection.
Q. -- among two other parameters you tested?
THE COURT: Overruled
A. Well, age would be one of the components.
Q. In paragraph 56 of your trial declaration, you discuss

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY , LTD. and GENPHARM, INC.,

Defendants.

New York, N.Y.
January 25, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

APPEARANCES

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JOHN S. GOETZ

because it sounded like you're asking me about four different questions at once.
Q. What I'm asking you is that in 1984, isn't it your belief that someone pursuing a promising lead would start with a molecule that demonstrates desirable efficacy and safety

properties and then try to find a better compound by investigating the structure-activity relationship around that molecule?
MR. VIOLA: Objection.
THE COURT: On what ground?
MR. VIOLA: They've objected to this witness as not being an expert, and he's just asking him his belief about what someone else would do in 1984.
THE COURT: Okay. I've understood these questions to be rooted in this witness' experience in 1984 in his development of pioglitazone. Is that your intention, counsel?
MR. BROWN: Yes, it is.
THE COURT: Okay. So I'll ask you to restate the question so that's clear.
BY MR. BROWN:
Q. In 1984, when you were pursuing a promising lead, was it your practice to start with the molecule that demonstrates desirable efficacy and safety properties and try to find a better compound by investigating the structure-activity relationship around that molecule?
A. In general, yes.
Q. And the goal of that was to try to determine what the optimal molecule would be?
A. The reason I'm hesitating is that it's not always possible to find the optimal molecule, but to find a molecule that

satisfied minimally acceptable criteria for development.
Q. In your experience, was that process of optimizing the properties of the molecule by structure-activity relationship the classic approach in medicinal chemistry in 1984?
MR. VIOLA: Objection.

THE COURT: Well, I'm happy to let you ask this witness this question, but it entirely undercuts objections, certain objections to his testimony. Go ahead.

I just want to advise you, you have about five minutes left.

THE WITNESS: Can you restate the question, please?

BY MR. BROWN:

Q. Doctor, isn't that process, namely, optimizing the properties of the molecule, the structure-activity relationship, the classic approach in medicinal chemistry in 1984?

A. It was a major approach in 1984.

Q. I'd like to go to Plaintiffs' Trial Exhibit 83.

MR. BROWN: And could we have the slide on that.

Q. It's tab 6 of your binder, I believe, and page 3 of that. And you've seen this document before, Doctor, is that correct?

A. Yes, I have.

Q. And we've just, we've prepared a version for the screen that just takes out the black and condenses them all together. And in this document, could you confirm for me that the portion

of the molecule that's being kept the same is shown at the top of the page? Is that correct?

THE COURT: Which exhibit -- I know it's 83, but what is this --

MR. BROWN: This is the A1534 report.

THE COURT: Thank you.

A. Well, the R isn't being kept the same, obviously, but the thiazolidinedione methyl phenyl ring is.

Q. And down the side of the page, the other portions of the molecule are being modified and altered to determine what impact structure has on activity, is that correct?

MR. VIOLA: Objection.

THE COURT: Sustained.

BY MR. BROWN:

Q. Dr. Morton, you are familiar with the toxicity testing that would be used by Upjohn management when considering whether to enter pioglitazone into the Upjohn development system, is that correct?

A. Yes, I was familiar.

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S. 59年 1 月 月報

名川主務 研究所長	提出日 S. 59. 1. 10

担当責任者： 藤田 剛	担当者（主研以上）： 松原 藤田

題　　名：抗血栓性薬剤の研究（1）（精原病に於ける）

(1) ADD-3195 構造化合物：予備毒性試験より急性毒性化合物について要約及び比較検討中。AD-4933≒AD-4974≒ADD-3195 >> ADD-3197 の順に強く、長期投与は ADD-3195 より弱く、ADD-3197 はほぼ同等の強さである。

[redacted]

(2) 有機合成を担当：ADD-3197 ラットのプロコンバリン刺激性インスリン分泌亢進作用をもつ インアルテルノリンなる性質と一緒に検討中

テーマ名（担当者）	特記事項（進捗状況・今後の方針等）	コメント・指示事項等
藤田	① ヒポスリージアン：凡検定より有効に作用した。	
	[redacted]	
	③ ADD-3195 構造化合物：予備毒性試験より急性毒性化合物の要約及び比較検討中。即ち AD-4933≒AD-4974≒ADD-3195 >> ADD-3197 の順に強く、長期投与は ADD-3195 より弱く、ADD-3197 はほぼ同等の強さである。	AD-4933 を第一候補として、ADD-3195 との要約書比較を検討する。
松原	④ 有機合成を担当：AD-3195 ラットのプロコンバリン(2%)に対するインスリン分泌亢進をする。 ⑤ ヒポスリージアン：ラットには高脂肪食で高血糖症より高血糖の予防を示した。 ⑥ ADD-3195 の投与を新薬担当への依頼：pain-free ラットに、高脂肪(10%, 20%)に於いても強く優れた血糖上昇抑制の効果を示した。	

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((Confidential)) (Form II)

January 1984 Monthly Report

Biology Lab Director Nagawa	Date of submission: 1/10/1984

Person responsible: Takeshi Fujita {seal: Fujita}	Persons assigned (Persons above the Chief Researcher level): Matsuo, Fujita

Summary: Study on metabolizing drugs (1) (diabetes treatment drug)
(1) ADD-3959 peripheral compounds: 4 compounds selected from the preliminary toxicity test were compared for their strength in drug efficacy and thoroughly examined. They were weak in this order: AD-4833 ≈ AD-4874 ≈ ADD-3894 >> ADD-3907, the first three samples exhibited about 5 times the strength of ADD-3878, and ADD-3907 exhibited nearly the same strength.

[Redacted]

(3) Non-obese type II diabetic model: Currently accumulating basic data on isopreterenol's reactivity to glucose-stimulating insulin secretion reaction in N-STZ rats, etc.

Name of theme (person assigned)	Special remarks (progress status, future policy, etc.	Comments, instructions, etc.
Fujita	(1) Primary screening: Effect was recognizable in 3 out of 16 samples. [Redacted] (3) ADD-peripheral compounds: Using KKA^y mice and SD rats, the efficacy strength of the 4 compounds selected from the preliminary toxicity test were thoroughly examined in terms of the blood glucose, NEFA, and TG lowering effects. AD-4833 ≈ AD-4874 ≈ ADD-3894 >> ADD-3907. The first three samples exhibited about 5 times the strength of ADD-3878, and ADD-3907 exhibited an equivalent strength.	Select AD-4833 as the first candidate, and study drug efficacy and toxicity comparison with ADD-3959.
Matsuo	(4) Non-obese type II diabetic model: N-STZ-1.5 and N-STZ-5 rats did not show an insulin secretion reaction to isopreterenol (iv). (5) Wistar fatty rats: In female rats, the high-starch diet caused the onset of hyperglycemia more frequently than did the high-sucrose diet (6) Effect of ADD-3959 on brown adipose tissue: direct effect on brown adipose tissue and weight increase was confirmed in pair-fed rats treated with a high dose (300 mg/kg, 2 wk) as well.	

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Certified Translation

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Certification

I, Sharon E. Nothman, do hereby certify the following:
I am fluent in the English and Japanese languages. I have translated and/or reviewed the translation of the Japanese document identified as:

TAK-00003970-39721L

and find it to be a true and accurate translation to the best of my knowledge and ability.

I affirm under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Signature: Sharon Nothman

Date: Aug 18, 2005

Sharon E. Nothman, President
Kotoba, Inc.
8417 Fenway Road
Bethesda, MD 20817

SA93

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Genpharm, Inc.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc Plaintiffs, v. Alphapharm Pty, Ltd., et al. Mylan Laboratories, Inc., et al. Watson Pharmaceuticals, Inc., et al. Ranbaxy Laboratories, Ltd., et al. Defendants.	(CONSOLIDATED) Civ. Action No. 04-CV-1966(DC)

DECLARATION OF HENRY I. MOSBERG

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SA94

QUALIFICATIONS 3

METHOD AND DOCUMENTS REVIEWED 6

OPINION 10

Pioglitazone Is Structurally Similar to the Lead Prior Art Compound 10

Pioglitazone has Properties Similar to the Lead Prior Art Compound 13

Given the Similarity in Structure and Properties, Pioglitazone is an Obvious Modification of the Prior Art Compound Alone 14

The Prior Art Sohda Article Provides Explicit Motivation to Make Pioglitazone 15

Routine Homologation Would Lead the Skilled Artisan from the Prior Art 6 methyl to Pioglitazone with a Reasonable Expectation of Success 19

Pioglitazone was the Natural Result of the Prior Art 6 methyl and Routine Homologation 27

The Results for Pioglitazone were Not Surprising 28

I, Henry I. Mosberg, of full age, declare pursuant to 28 U.S.C. § 1746 that:

1. I have been retained as an expert consultant to the law firm of Frommer, Lawrence and Haug, LLP, to provide an expert opinion in this matter on the question of whether the compound known as pioglitazone was obvious to those skilled in the art prior to the date Takeda filed its patent application specifically covering this compound. Takeda's pioglitazone patent issued as United States patent 4,486,777. I will refer to this patent throughout this trial declaration as the '777 patent. I have been asked to provide the Court with this declaration in lieu of my testimony on direct examination.

QUALIFICATIONS

2. I am an expert in the field of medicinal chemistry, and can provide testimony that will assist the Court in rendering a verdict on what persons of ordinary skill in the art of medicinal chemistry would do had they reviewed the relevant prior art in this matter. The bases for my qualifications as an expert are set forth as follows:

a. **Education:** I received my B.S. in Chemistry from the University of Illinois, Chicago in 1971 and my Ph.D. in Biophysical Chemistry from the University of Illinois, Urbana in 1976. Biophysical chemistry is an interdisciplinary field which aims to rigorously quantify the physical and chemical principles governing biological systems.

b. **Academic Duties:** I joined the faculty of the University of Michigan, Department of Medicinal Chemistry in 1983 and have held the rank of Professor there since 1995. The field of medicinal chemistry is a subset of Chemistry and seeks to uncover the precise chemical mechanisms of action in animals which ultimately lead to the development of useful pharmaceutical agents, principally for human beings. Since 1999, I have served as Associate Dean of Research and Graduate Education where some of my responsibilities are promoting and

facilitating external funding opportunities, overseeing internal funding mechanisms, and allocating research space. I have served on the Medicinal Chemistry Program Committee at the University of Michigan since 1986. The Committee addresses the graduate curriculum and degree requirements in Medicinal Chemistry. As either an assistant or full Professor at the University of Michigan, I have taught numerous undergraduate and graduate courses dealing with medicinal chemistry concepts, drug design and "lead optimization." Lead optimization is the method by which medicinal chemists slightly modify or "tweak" the structures of a promising chemical compound, known as a "lead," to maximize its potency and/or minimize toxicity or unwanted side effects. Drug synthesis is the method by which those structural changes are made to the lead.

c. **Publications:** I have authored or co-authored 142 peer-reviewed articles relating to the issues of drug design, including lead optimization, drug synthesis, and drug mechanism of action. The specific articles I have authored or co-authored are set forth in my up-to-date curriculum vitae, Alphapharm Trial Exhibit 14 (Exhibit A to this Declaration). The articles appear on pages 4 through 14 therein.

d. **Awards:** In 2005, I was awarded fellowship status with the American Association for the Advancement of Science (AAAS), the world's largest general scientific organization. Fellowships in AAAS are highly competitive, and are only awarded to a select few within a discipline once a year. In 1989, I was awarded a NIDA Research Scientist Development Award in support of research toward understanding the structural requirements for selective opioid compounds. In 1973 and 1977, I received pre-doctoral and post-doctoral fellowships respectively with the National Institute of Health (NIH), one of the world's foremost medical research organizations. My pre-doctoral fellowship concerned NMR studies of the mechanism

of the enzyme aspartate transcarbamylase. My post-doctoral fellowship concerned metal binding properties of the peptide antibiotic, bacitracin A.

e. **Editorial Boards:** I presently serve on the editorial boards of two journals, *Biopolymers-Peptide Science* and *The Journal of Peptide Research*, and have recently completed a four year term on the editorial board of the *Journal of Medicinal Chemistry*. On those editorial boards, I have provided, and continue to provide, "peer review," that is, I review submitted manuscripts to determine whether the science supporting them is valid, complete, and merits publication in the journal. Articles lacking in adequate support are rejected. I am a Senior Associate Editor of the new journal, *Chemical Biology & Drug Design*, which will launch in 2006. In this capacity I will be making higher-level editorial and content decisions with authors, in addition to coordinating with other peer-reviewers for the proposed articles. I also serve as an ad hoc reviewer for organizations such as NIH, the National Science Foundation, the Medical Research Council of Canada, Research Corporation, the Science Foundation of Ireland, and the Human Frontier Research Fund.

f. **Specific Drug Design Experience:** I have specifically engaged in the process of drug design and lead optimization on at least 10 different compounds, including the investigation of structure-function relationships of several opioid peptides and non-peptides, the development of inhibitors of RGS protein-mediated termination of G protein activation (with potential as a novel class of drugs), and the development of peptide inhibitors of platelet activation, with potential value for prevention of heart attacks and strokes. Peptides are a chain of amino acids which serve critical biological functions. Insulin, used naturally in the body to lower blood glucose, and used for the specific treatment of diabetes, is one of a vast array of biologically important peptides. Over the years, I have been awarded extramural grants by NIH

and other agencies for all of this work. The currently active NIH research grants on which I am the principal investigator or co-principal investigator are set forth in page 3 of Alphapharm Trial Exhibit 14 (Ex. A to his Declaration). My work has resulted in three issued patents covering the optimized peptide compounds, and a pending application covering a fourth such compound.

g. **Previous Certification as an Expert:** I was accepted as an expert in medicinal chemistry in the United States District Court for the District of Massachusetts in September, 2005. I provided the court there with an expert tutorial in medicinal chemistry. The case in which I testified is known as *Aventis Pharma Deutschland Gmbh and King Pharmaceutical v. Cobalt Pharmaceuticals, Inc.*

METHOD AND DOCUMENTS REVIEWED

3. The '777 patent (Alphapharm Trial Exhibit 7, attached to this Declaration as Exhibit B) is directed to thiazolidine derivatives of a particular formula which "exhibit in mammals blood sugar- and lipid-lowering activity, and are of value as a therapeutic agent for treatment of diabetes and hyperlipidemia." (Alphapharm Trial Exhibit 7, Preamble) Prior art references within, and reasonably pertinent to, this field of endeavor were relevant to me on the question of whether a person of ordinary skill would have found the pioglitazone compound obvious in light of this art.

4. I was made aware that Takeda employees, years before the '777 patent was applied for, published the results of studies they had conducted on thiazolidine derivatives with anti-diabetic properties, such as lipid and blood glucose-lowering effects. I was also made aware that Takeda's inventors sought and received several issued patents concerning the same subject matter. I requested that Frommer Lawrence and Haug provide all of those publications, patents and publicly-available prosecution histories to me. I also requested the '777 patent itself, the application for which was filed on January 17, 1986.

5. I received from Frommer Lawrence and Haug a packet of prior art materials that included the following:

a. United States Patent 4,287,200 (the "'200 patent"), issued in the United States on September 1, 1981 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 1 [Exhibit C, attached)];

b. Application No. 62,512, the Prosecution History associated with the '200 patent, the application for which was filed on July 27, 1979 (Alphapharm Trial Exhibit 2 [Exhibit D, attached)];

c. Sohda, T. et al., "Studies on Antidiabetic Agents. II.1 Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives," *Chemical and Pharmaceutical Bulletin* 30:10 (October, 1982) 3580-3600 (Alphapharm Exhibit Alphapharm Trial Exhibit 3 [Exhibit E, attached)].

d. United States Patent No. 4,340,605 issued in the United States on July 20, 1982 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 4 [Exhibit F, attached)];

e. United States Patent No. 4,444,779, issued in the United States on April 24, 1984 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 5) [Exhibit G, attached];

f. Application No. 476,017, the Prosecution History associated with the '779 patent, the application for which was filed on March 15, 1983 (Alphapharm Trial Exhibit 6 [Exhibit H, attached]).

Alphapharm trial exhibits 1 through 6 all concern thiazolidine derivatives with anti-diabetic properties, such as lipid and blood glucose-lowering effects. Each describes and/or teaches thiazolidine derivatives with structures more or less similar to pioglitazone. The '200 (Alphapharm Trial Exhibit 1), '605 (Alphapharm Trial Exhibit 3) and '779 (Alphapharm Trial Exhibit 5) patents and their respective prosecution histories all set forth the activities of the United States Patent Office, an agency of the United States government. In addition to its appearance in the prior art and my reliance on it for my opinions, the Sohda article (Alphapharm

Trial Exhibit 2), noted in 6c. above, was published in what I know is a reliable periodical relating to chemistry and pharmaceutical science.

6. Other than the prior art listed above, I also received from Frommer Lawrence and Haug the following documents relevant to my inquiry:

a. the '777 patent (Alphapharm Trial Exhibit 7) [Exhibit B, attached];

b. a letter from Frommer Lawrence and Haug attorney Kevin Murphy to Barbara Moore, litigation counsel to Takeda, dated July 8, 2005 (Alphapharm Trial Exhibit 8) [Exhibit I, attached];

c. portions of the transcript of Takeda employee Hiroyuki Odaka, dated March 24, 2005 ("Odaka Deposition," Alphapharm Trial Exhibit 9) [Exhibit J, attached];

d. an article by, Cunningham, S. et al., entitled "The Characterization and Energetic Potential of Brown Adipose Tissue on Man," *Clinical Science* 69 (1985) 343-348 (Alphapharm Trial Exhibit 10) [Exhibit K, attached]; and

e. the results of Takeda's drug design work on structural analogs to pioglitazone found in Fujita, T., "Pharmacological Actions of Selected Compounds in Normal and Diabetic Animals," Takeda Biology Laboratories, January 1984 (Alphapharm Trial Exhibit 11) [Exhibit L, attached].

7. The '777 patent, like the other patents above, sets forth the activities of the United States Patent Office. It covers formulas of the compound of interest. Broadly, these compounds are what I would term ethylated pyridyl thiazolidine derivatives. The letter from Frommer Lawrence and Haug detailed for me that Takeda only claimed that Alphapharm infringed claims 1, 2 and 5 of the '777 patent, so I confined my obviousness analysis to those claims. I am familiar with the signature of Kevin Murphy and his signature appears on the signature line of Alphapharm Trial Exhibit 8. I used Alphapharm Trial Exhibit 10, the Cunningham article, to educate myself about how persons of ordinary skill would respond to brown fat results in the 1980s. That article was published in *Clinical Science*, a well-recognized and reliable journal

relating to health and disease. I similarly reviewed Takeda's actual drug design work in Alphapharm Trial Exhibit 11 as a check on my analysis of what others of skill in the art would do. Alphapharm Trial Exhibit 11 represents statements made by Takeda's scientist, Takeshi Fujita, concerning the scope of Takeda's drug development, made while Dr. Fujita was employed by Takeda. As a drug developer for Takeda, Dr. Fujita's report was made within the scope of his employment.

8. To further educate myself, I performed my own research on what persons of ordinary skill in the art were doing in the field of drug design at or before the time of Takeda's alleged invention. That research uncovered the following article:

- Nohara, A. et al., "Studies on Antianaphylactic Agents. 6.1 Synthesis of Some Metabolites of 6-Ethyl-3(1H-tetrazol-5-yl)chromone and their Analogues," *Journal of Medicinal Chemistry* 22:3 (1979) 290-295 (Alphapharm Trial Exhibit 12) [Exhibit M, attached].

This article detailed that persons of ordinary skill in the art—including Takeda—had practiced the synthesis of routine homologues to improve promising drug compounds. Had the same method been applied to the lead compound that emerged from the prior art, it would have led naturally to the relevant formulas claimed in the '777 patent. I relied on these articles as prior art as well as background, and can attest that the *Journal of Medicinal Chemistry* is a well-recognized, reliable periodical concerning medicinal chemistry.

9. Persons of Ordinary Skill in the Art: I endeavored to analyze the prior art—not from my own considerable experience as a medicinal chemist—but from the standard of a person of *ordinary* skill in the art. On this issue, I looked carefully at what the above patents covered, the issues involved in synthesizing experimental pharmaceutical compounds generally, and the average educational level of drug developers. The person of ordinary skill for the art presented in this case would generally have a combination of training and experience. For example, a

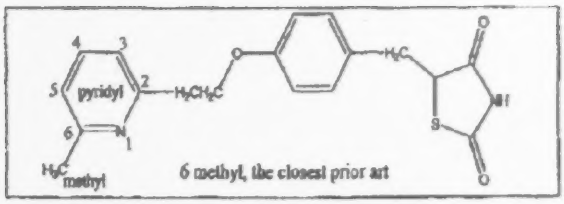
typical person of ordinary skill in this art would have secured her Ph.D. in medicinal chemistry or a related field, done postdoctoral work for two to three years and thereafter secured a position with a pharmaceutical company. After two or three years there, she would have achieved the necessary training and experience to qualify as a person of ordinary skill.

OPINION

10. I was retained as an expert in June 2005 in this matter. As I noted above, my task was to determine whether persons of ordinary skill in the art of medicinal chemistry would, after reviewing the available prior art before Takeda filed the '777 patent application, be led naturally to the pioglitazone compound with minimal experimentation. After my review of this art—and in particular, the early publication of a close structural analog to pioglitazone—it is my considered opinion that Takeda did not invent anything in the '777 patent. Persons of ordinary skill in the art would have recognized as early as 1982—nearly 4 years before Takeda filed its application—the very real promise of this close structural analog, and performed the few and quite routine experiments in drug design necessary to "tweak" it and reach the invention. Persons of ordinary skill would have undertaken this task with a reasonable expectation of success.

Pioglitazone Is Structurally Similar to the Lead Prior Art Compound

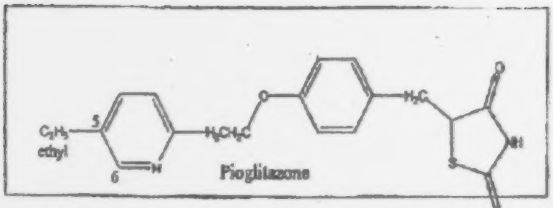
11. In my review of the prior art, I noted that as early as September 1, 1981, Takeda disclosed in Alphapharm Trial Exhibit 1[C, attached], the '200 patent, a compound it called a "novel thiazolidine derivative having hypolipidemic [i.e, lipid-lowering] and hypolglycemic [sic, i.e., blood-glucose lowering] activities with low toxicity." Alphapharm Trial Exhibit 1, col. 1, lines 4-6. The compound appears in Alphapharm Trial Exhibit 1 at column 13 and is listed as compound 42. That compound is known as a 2 "pyridylmethyl" with a "methyl" at the 6 position on the "pyridyl" ring. Compound 42 has this structure:



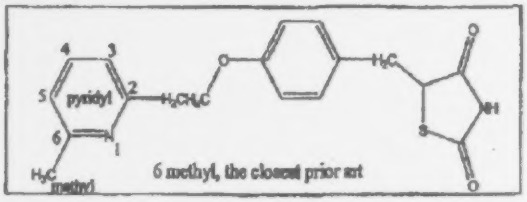
6 methyl, the closest prior art

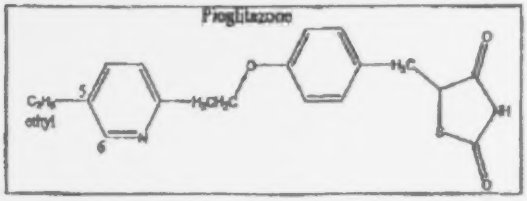
12. I have set forth in red the left-most portion of compound 42, which I will call the left-most "moiety." A moiety is a portion of the molecule of interest. Despite the color-change, the above diagram is a full and accurate depiction of the compound disclosed as compound 42 in the '200 patent. The left-most moiety consists of a "pyridyl" ring with a "methyl substituent" at position 6. "Pyridyl" denotes a planar six-membered ring of 5 carbon atoms and one nitrogen atom. Because carbon atoms are so common in organic chemistry, they are often represented by mere points of intersection, rather than the letter "C", where they appear. For ease of reference, any moiety attached to a ring, known as a "substituent," is given a particular number corresponding to the position on the ring to which it is attached. Chemists start numbering the ring's positions with the highest atomic weight atom in the ring. In this instance, nitrogen bears a higher atomic weight than carbon, and thus would be numbered "1." In the example above, numbering proceeds in counterclockwise fashion so that the 2 position has the CH_2CH_2O substituent. Thus—following that pattern– the CH_3 substituent, known as a "methyl," in the location above is called a 6 methyl. Because this compound is so similar to pioglitazone, I will refer to it from here on simply as the "6 methyl."

13. The compound known as pioglitazone, which Takeda first claims in the '777 patent, has a very similar chemical structure to the earlier-disclosed 6 methyl. Indeed, it is an analog of the closest prior art. Pioglitazone has the formula:



Pioglitazone is claimed in dependent claim 2 of the '777 patent, Alphapharm Trial Exhibit 7. There are only two differences between pioglitazone and the 6 methyl. Takeda substituted an ethyl (C_2H_5) for the methyl (CH_3) and linked that substituent at the *5* position instead of the 6 position, as shown below:





Claims 1 and 5 of the '777 patent are even closer to the prior art 6 methyl compound because they both claim the ethyl (C_2H_5) at *any* position, including the 6 position. Alphapharm Trial Exhibit 7, claim 1. Notably, claim 4 of the '777 patent (not at issue here), in fact, specifically claims the ethyl (C_2H_5) at the 6 position.

14. Moreover, Takeda admitted that pioglitazone is structurally "similar" to other methyl substituents at the 3, 4 and 5 positions on the pyridyl ring in the '777 patent. Alphapharm

Trial Exhibit 7, col. 5, l. 64-68. If pioglitazone is similar to methyl substituents at positions 3 and 4, it stands to reason that it is "similar" to a methyl substituent at the 6-position as well.

Pioglitazone has Properties Similar to the Lead Prior Art Compound

15. Compounds that share similar structure often share similar properties. And given the structural similarities between the closest prior art compound and pioglitazone, the skilled artisan would not be surprised that the two compounds share similar properties.

16. Pioglitazone shares many properties with the prior art 6 methyl. Pioglitazone "exhibit[s] in mammals blood sugar-and lipid-lowering activity, and [is] of value as a therapeutic agent for treatment of diabetes and hyperlipidemia." Alphapharm Trial Exhibit 7, Preamble. The '777 also asserts that the claimed ethylated thiazolidine derivatives, including pioglitazone, "can be practically used as antidiabetic agents . . . ." Alphapharm Trial Exhibit 7, col. 1, line 36.

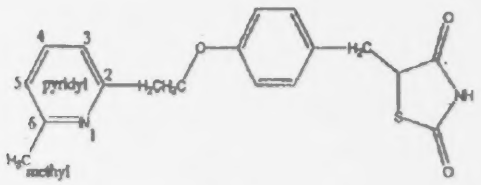
17. Similarly, according to the '200 patent, the prior art 6-methyl was "useful as, for example, remedies for diabetes, hyperlipemia and so on . . . ." Alphapharm Trial Exhibit 1, Abstract. In fact, Takeda claimed this compound, along with others, possessed "hypolipidemic [i.e, lipid-lowering] and hypolglycemic [sic, i.e., blood-glucose lowering] activities with low toxicity." Alphapharm Trial Exhibit 1, col. 1, lines 4-6. Moreover, when the inventors of the '200 patent were faced with a rejection by the Patent Office indicating that all of the compounds were obvious in light of an earlier patent disclosing thiazolidine compounds, the inventors' attorney responded that "the claimed compounds are superior to the known compounds of the cited [Diamond] reference in various pharmaceutical activities, such as hypolipidemic activity, pypoglycemic [sic] activity, etc." Alphapharm Trial Exhibit 2 at Alpha 70 to 71. As part of the response to the rejection, Takeda inventor Takeshi Fujita signed a declaration comparing the blood glucose and lipid-lowering effects of 9 of the compounds taught in the '200 patent,

including the 6 methyl, against those of the Diamond reference. Alphapharm Trial Exhibit 2 at Alpha 75 & 77.

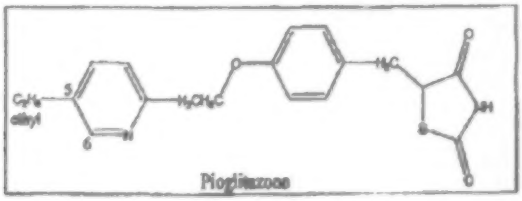
18. The Fujita declaration in the prosecution history of the '200 patent is significant for another reason. It provides motivation to one of skill in the art to pursue further examination of the 6 methyl. As noted above, the prosecution history of the '200 patent—which itself is publicly available and would be considered by one of skill in the art—compares the blood glucose and lipid-lowering properties of 9 of '200 patent compounds. One of those compounds was the 6 methyl. As the skilled artisan would readily appreciate upon review of this comparison, the six methyl was statistically superior to 6 of the 9 compounds relied upon. The superior efficacy of the 6 methyl would motivate one of skill in the medicinal chemistry art to make antidiabetic compounds having a structure similar to this very efficacious chemical structure.

Given the Similarity in Structure and Properties, Ciglitazone is an Obvious Modification of the Prior Art Compound Alone

19. On September 1, 1981 the '200 patent made three facts known to those of ordinary skill in the art of medicinal chemistry. First, a new compound existed with this formula:



Second, this new compound was useful as a remedy for diabetes. Third, of the numerous compounds disclosed, *the 6 methyl had the highest level of efficacy*. Based solely on these facts—made publicly available by the '200 patent and its prosecution history—one of ordinary skill in the art would have been motivated to search for new diabetic drugs and in that search would have been motivated to make compounds having similar structure and properties as the prior art 6 methyl, including this compound:



Pioglitazone

Simply put, given *only* the disclosure of the '200 patent and its prosecution history, pioglitazone is an obvious modification of the prior art 6 methyl.

The Prior Art Sohda Article Provides Additional Motivation to Make Pioglitazone

19. A year after the issuance of the '200 patent, Takeda published the results of its study of 101 thiazolidine compounds using the same testing parameters set forth in the Fujita declaration of the '200 patent: blood glucose- and lipid-lowering effects. Alphapharm Trial Exhibit 3 (I will term this prior art reference, the "Sohda Article" from here on). The authors measured potency, for each of the two effects, on a scale of 0-4, with 4 being the most potent, and presumably the most-promising, as a potential antidiabetic pharmaceutical compound.

20. The 6 methyl is listed as compound 58 in Alphapharm Trial Exhibit 3 on page 3586. It ranked a "3" in blood glucose-lowering and a "4" in lipid-lowering. Of the 101 compounds considered, only 6 other compounds scored as well. That the 6-methyl ranked in the top ~5% of the group in terms of desired effect is strong motivation to select it as a compound to

further study. Those of ordinary skill in the art of medicinal chemistry are today—just as they would be then—motivated to pursue new, more potent, drugs based on known drugs with favorable characteristics. Indeed, this was precisely the motivation for the Sohda article itself. The authors explain: "Since compound 1 (AL-321) [the known drug] was first found to possess potent hypoglycemic and hypolipidemic activities, various compounds having modified phenethyl moieties . . . have been synthesized." Alphapharm Trial Exhibit 3 at 3588. Standing alone, the high activity of the 6 methyl provides as strong motivation to select compound 58 as a "lead" compound for further testing.

21. In addition to the high score for desired effect, the Sohda article provides still further motivation to make incremental changes to the 6 methyl. The authors note that the 6 methyl compound "caused considerable increases in body weight and brown fat weight." Alphapharm Trial Exhibit 3 on page 3589. Perceiving this as a problem with a known potent compound would motivate one of skill in the art to make changes. The authors of the Sohda article themselves were motivated to attempt small structural changes to a known potent compound because it had slightly undesirable characteristics. The authors note:

> Among the compounds listed in Tables I and II, compounds 10, 12, 15, 18 and 25 showed more potent activities than 1, but these compounds caused considerable increases in relative liver weight and liver lipid at high dose levels or on chronic administration. As this undesirable effect may have been a consequence of the existence of two benzene rings in the molecule, we replaced one of them with other moieties.

Alphapharm Trial Exhibit 3 at 3588. The skilled artisan would be similarly motivated to attempt further substituent replacement to maintain the very desirable potency of the 6 methyl, while reducing the unwanted side effects of increased body weight and brown fat weight.

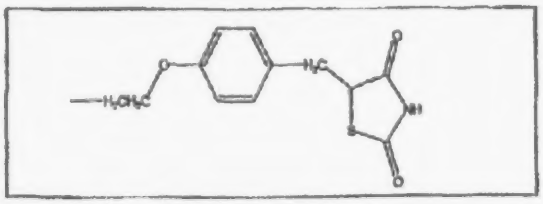
22. Furthermore, persons of skill in the art would have noted in their review of the Sohda article that the compounds containing pyridyl rings on the 'left hand side' of the structure (compounds 50-60) display high potency. It would have been further noted that of these compounds, the 6 methyl compound (compound 58)—the *only* example in this series with a substituent on the pyridyl ring—was the most potent. One of ordinary skill in the art—realizing that the 6 methyl substituent was responsible for increasing potency in the series—would thus have been *strongly* motivated to attempt further substituent replacement to maintain the very desirable potency of the 6 methyl, while reducing the unwanted side effects.

23. Moreover, the unwanted side effects observed for the 6 methyl compound would in no way have suggested that it was not worth tweaking. In fact, less than two years after the Sohda article appeared—and more than a year *before* the inventors filed the application for the '777 patent—the person of ordinary skill in the art would have learned that Takeda had *specifically claimed* the 6 methyl compound in claim 4 of the '779 patent. Alphapharm Trial Exhibit 5, col. 20, ll. 43-45 (claim 4). Thus Takeda itself published to the world in the '779 patent that substituted pyridyl rings, such as the 6 methyl, were novel and useful in the treatment of diabetes. Furthermore, in the prosecution history of the '779 patent, Takeda admitted that the 6 methyl had been claimed because this compound had become "important." Alphapharm Trial Exhibit 6, at Alpha 54.

24. But even if Takeda had not published that it was zeroing in on substituted pyridyl rings, the whole point of drug design is to maximize potency while minimizing toxicity following the most straightforward possible path. A person of ordinary skill in medicinal chemistry would have considered increases in brown fat and weight gain in test rodent to be at

worst unwanted, potential side effects, and would have proceeded to minimize them accordingly while preserving potency in the 6 methyl.

25. The motivation to minimize these side effects through systematic incremental changes to the 6 methyl is even stronger when the undesirable increases in body weight and brown fat weight are coupled with the authors' disclosure that "the partial structure (shown below)



is the essential structural feature for both glucose- and triglyceride-lowering activities." Given this, the person having ordinary skill would even more readily understand that discreet, and simple, modifications to the "pyridyl" ring of the 6 methyl—the moiety *not* responsible for the desired glucose- and triglyceride-lowering properties—would be expected to, successfully, affec the body weight and brown fat weight increases.

26. Finally, the Sohda article revealed the increased efficacy of the pyridine compounds when adding a methyl substituent to the unsubstituted pyridyl, compound 57 in the article. Triglyceride lowering activity increased by at least 40% as a result of the addition of a methyl group. The increase in efficacy was a consequence of the specific physicochemical effects on the molecule (e.g. increased lipophilicity) which occur when adding a CH_2 group. As Adding another CH_2 would further increase these effects on the compound and in following the trend of homologation, potentially increase activity. The Sohda article demonstrated a clear

trend and provided the motivation to perform routine homologation on pyridine rings with an expectation of improving the compounds profile.

27. While the '200 patent and file history discloses the 6 methyl compound, its usefulness, and its superior efficacy—which is enough by itself to render pioglitazone obvious to one of ordinary skill—the subsequent Sohda article is the key piece of prior art that the skilled artisan would look to. It not only discloses all of the facts disclosed by the '200 patent and file history but also provides further, multiple, explicit motivation to use the 6 methyl to obtain pioglitazone. Thus, although either the '200 patent and file history or the Sohda article—standing alone—render pioglitazone obvious, the Sohda article is particularly significant in this respect.

Routine Homologation Would Lead the Skilled Artisan from the Prior Art 6 methyl to Pioglitazone with a Reasonable Expectation of Success

28. In addition to these disclosures, however, it is important to consider the common knowledge in the medicinal chemistry art at the time of the invention. Specifically, it was known to focus on a "lead compound" and "tweak" it to result in a more effective and less toxic drug. A "lead" compound is a compound that has the desired activity but has some deficits, including unwanted side effects or toxicity. Development of the lead, then, is to maintain or improve the desired activity while reducing or eliminating the undesired activity, such as the authors' concerns about increases in brown fat or weight gain.

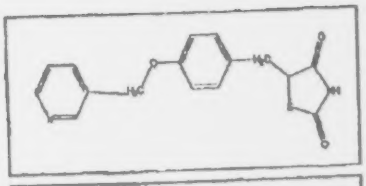
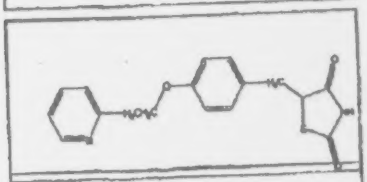
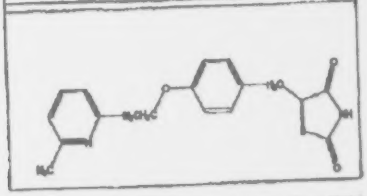
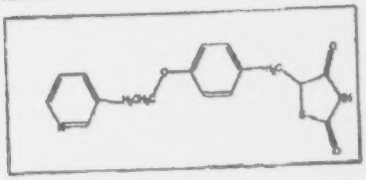
29. One of ordinary skill in the art of medicinal chemistry reviewing the prior art—either the '200 patent or the Sohda article—would have been motivated to select the 6 methyl as the "lead" compound for further testing. One skilled in the art of medicinal chemistry would have been motivated to "tweak" the 6 methyl to maximize its effectiveness by altering the position of the methyl on the pyridyl ring ("walking the methyl around the ring") and by

substituting an ethyl (C_2H_5) for the methyl in the available positions on the pyridyl ring. This latter process is called homologation, and is a routine procedure in lead optimization. Homologation, the stepwise lengthening of a substituent by addition of methylene units (CH_2), is based on the well-observed observation that such conservative modifications (such as an ethyl substituent replacing an methyl substituent) often result in improved potency or diminished toxicity. The nearest "relative" in the organic chemistry family to a methyl (CH_3) is an ethyl (C_2H_5). Though there is no absolute predictability in the field of medicinal chemistry, any person of ordinary skill in the art would have had a reasonable expectation of success in "tweaking" the lead compound in this way.

30. The skilled medicinal chemist would not proceed randomly, but would base his attempts on the available knowledge of prior research techniques and literature used in his field. Given the disclosures of the Sohda article, such a person would have recognized that the most straightforward course would have been conservative modifications to follow-up the observed potency-enhancing 6 methyl substituent: 1) examination of methyl substituents at the unexplored 3, 4 and 5 positions and 2) examination of the ethyl homologs at the same positions and comparison of the results of each substituent in test subjects.

31. Thus, the first step that any ordinarily skilled medicinal chemist would take in "tweaking" the 6 methyl would be to vary the position of the methyl (CH_3) substituent, in essence to "walk" the favorable substituent around the pyridyl ring. Such a step is taken with the expectation that the methyl substituent is causing the potent activity, but the position of the methyl on the ring (at the 6 position) may be causing the unfavorable side effects. That the methyl substitution increases potency follows directly from the published data in the Sohda article. There, the person of ordinary skill would observe the following values:

SA113

Compound	Structure	Total Potency
56		6 (3 and 3)
57		5 (3 and 2)
58		7 (3 and 4)
59		5 (3 and 2)

All, according to the article, "showed potent activities [but] they, especially 57 and 58, caused considerable increases in brown fat and weight gain." Alphapharm Trial Exhibit 3, at p. 3589. One of skill in the art would deduce from these data that the methyl substituent was responsible for the potent activity, particularly in that none of the others showed comparable values. Varying its position would be the first—but not the only—option to minimize these unwanted effects. Persons of ordinary skill in the art would synthesize and test methyl substituents at the 3, 4, and 5 positions on the pyridyl ring and compare their efficacy and toxicity results to that found

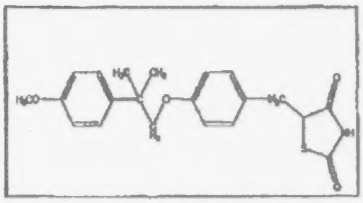
with the 6 methyl. A fair and accurate portrayal of the resulting structures can be found at Alphapharm Exhibit 281 [Exhibit N, attached].

32. The second route—which would probably but not necessarily be taken simultaneously—would be to synthesize and test homologs of the methyl-substituted pyridyls by switching to ethyl substituents at the same positions. Such small structural changes often have significant effects on potency or side effects due to subtle, predictable changes in the solubility and size of the molecule. The ability of such homologation to yield improvements in the activity profile in a series of compounds was well known at the time of the Sohda II article.

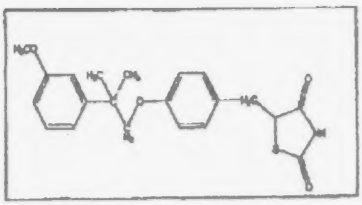
33. These are the only steps required to reach the alleged "invention" of pioglitazone, and encompass a total of only seven synthesized and tested compounds, in addition to the lead 6 methyl compound: the 5 methyl vs. the 5 ethyl (pioglitazone), the 4 methyl vs. the 4 ethyl, the 3 methyl vs. the 3 ethyl, and the 6 ethyl. Success was not dependent upon random variations of numerous parameters. Rather, the prior art instructed one skilled in the art to perform these steps in this particular order to arrive at pioglitazone. These choices are hardly surprising; they are in fact expected, and anyone of skill in the art would have made them. Furthermore, there are no intermediate compounds involved in the synthesis of pioglitazone which could potentially teach away from the desired compound.

34. Walking the favorable substituent around the ring to examine positional effects was known well before Takeda filed the application which issued as the '777 patent. Indeed, the '200 adopts the concept. There, Takeda examined the effect of "walking" a methoxy (CH_3O) substituent around a phenyl ring, respectively occupying the 4, 3 and 2 positions on the described phenyl ring. Alphapharm Trial Exhibit 1 ('200 Patent), example compounds 31, 32, & 33. Examples 18 and 19 also demonstrate the same concept with methoxy (CH_3O) substituents at

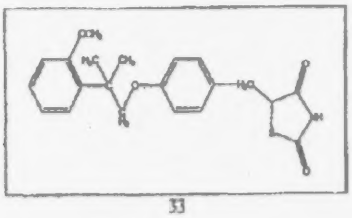
positions 2 and 4 on the phenyl ring. These examples are set forth completely and accurately below for ease of reference:



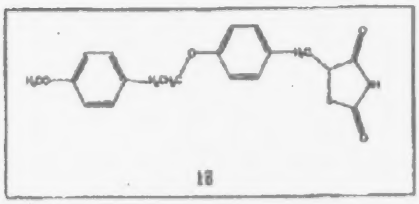
31



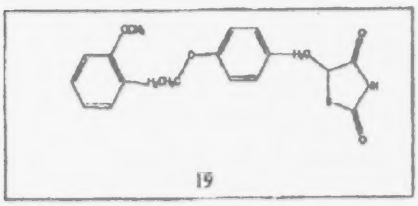
32



33



18



19

The effect of a chloro (Cl) substituent at different positions on a phenyl ring was examined in compounds 1 and 2.

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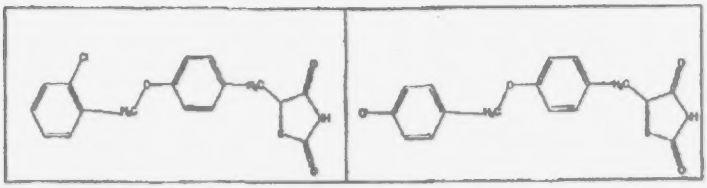
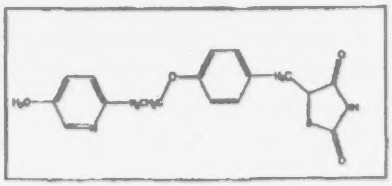
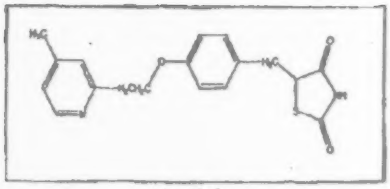


1 2

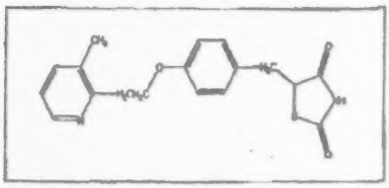
35. Internally at Takeda, once the high efficacy of the 6 methyl was known, synthesizing and testing methyls at alternate positions had a high priority, as it would have to others of ordinary skill in the art. This point is illustrated by Takeda's own internal documents that demonstrate the evaluation of methyl at various positions on the pyridyl ring. Alphapharm Trial Exhibit 11 (TAK 00117925). Takeda researchers, armed with the same knowledge available to the public regarding the efficacy of the 6 methyl, took the next logical step and "walked" the methyl substituent around various positions on the pyridyl ring and subsequently tested these compounds to see if this slight structural modification improved the overall profile as compared to the 6 methyl. Takeda's own synthesis efforts as reported in that 1984 Takeda document are set forth completely and accurately below:



5 methyl



4 methyl

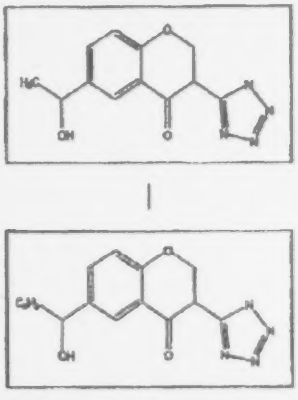


3 methyl

36. The '200 and the '779 patents each speak in terms of "alkyl" substituents and components, alkyls being linear chains of carbon atoms singly bonded to other carbon atoms or hydrogen atoms. Alphapharm Trial Exhibit 1 ('200 patent at claim 1) and 5 ('779 patent at claim 1). In medicinal chemistry, the most common examples of alkyls are methyl (CH_3) and ethyl (C_2H_5). Takeda took the same position, referring in the '200 and '779 patent specification to the substituents on ring systems, "examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.)." Alphapharm Trial Exhibit 1, '200 patent, col. 2, l. 45 & Alphapharm Trial Exhibit 5, '779 patent, col. 2, l. 45. Takeda's choice of language suggests that among the alkyls methyl and ethyl substituents may be preferred. Indeed, in its prosecution of the '779 patent, the applicant specifically represented that the new class of substituents to be claimed in the '779 patent was a "relatively ***narrow*** and ***well-defined group*** of constituents" that "would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." Alphapharm Trial Exhibit 6, Alpha 60-61. It would hardly come as a surprise therefore that an

ethyl substituted pyridyl could be selected from the '779 patent claim 1 genus. Pioglitazone as claimed in the '777 patent is merely an obvious species of the '779 genus.

37. Further, Takeda itself recognized the standard use of homologation in drug development eight years before it applied for the '777 patent. In 1978, Takeda researchers published the results of studies on anti-anaphylactic agents. Alphapharm Trial Exhibit 12, (the "Nohara article," after its lead author). After identifying a lead compound with the ethyl substituent C_2H_5 at the 6 position on a phenyl ring, the researchers identified seven metabolites. Takeda synthesized and tested for biological activity several metabolites as well as analogs of two metabolites, 2 and 3. A total of 28 compounds were synthesized to reference against the lead compound. Metabolite 2 is of particular interest. That metabolite consisted of a methyl group attached to a carbon which linked a hydroxyl group to the phenyl ring. Below is a fair and accurate example of the metabolite disclosed in the Nohara article:



38. In addition to synthesizing and testing metabolite 2, Nohara et al. also examined homologous compounds including compound 14a (the ethyl homolog of compound 2). This methyl to ethyl homologation is exactly as practiced in the '777 patent and demonstrates that

such an approach was routine in the art at that time. In fact, Nohara et al did not even bother to explain why the methyl was replaced with an ethyl analog, since the decision to do so is routine in the industry and therefore did not require an explanation when peer reviewed.

39. Indeed, as noted above, many examples provided in the '200 patent demonstrate that Takeda was aware that substitution of a methyl with an ethyl should be carried out to test for useful compounds. Compound 3 in example 9 is the same compound as example 4, except that the methyl substituent CH_3 in compound 3 was replaced with the ethyl substituent, C_2H_5, in compound 4. Alphapharm Trial Exhibit 1 ('200 patent) at col. 8. Compounds 5 through 9 continue the homologous series and demonstrate considerable thoroughness in exploring the effect of chain length. Alphapharm Trial Exhibit 1 ('200 patent) at cols. 8-9. Takeda practiced the same methyl-ethyl substitution on an aromatic ring in compounds 15 and 16. Alphapharm Trial Exhibit 1 at col. 9. These are the exact replacements which led to the claimed invention in the '777 patent. In fact, compounds 15 and 16 of the '200 patent share the same structural relationship as c and I of the '777 patent, differing only in having a substituted phenyl ring rather than a substituted pyridyl ring.

Pioglitazone was the Natural Result of the Prior Art 6 methyl and Routine Homologation

40. In the context of drug design, the replacement of a methyl substituent at four locations on a pyridyl ring with the next natural replacement hardly constitutes extensive experimentation, especially when following up a promising lead such as the 6 methyl. Takeda itself had taught the necessity to make all related compounds, by publishing so many analog examples both in its patents and the literature. Once that obvious ethyl-substituted series of compounds were synthesized and tested on the pyridyl ring, anyone skilled in the art would have determined that the series had superior blood-glucose lowering and triglyceride lowering activity with "extremely low toxicity" as reported in the '777 patent specification.

The Results for Pioglitazone were Not Surprising

41. While prosecuting the '777 patent, the inventors attempted to show that the potency and toxicity results for pioglitazone were nevertheless surprising—and thus not obvious—relative to the structurally similar compounds with methyl substituents at the 6, 5, 4 and 3 positions on the pyridyl ring. Alphapharm Trial Exhibit 7, Table I, cols. 5-6. The prior art 6 methyl proved more potent than pioglitazone but the inventors instead asserted that pioglitazone had "extremely low toxicity" as compared with the 6 methyl. Alphapharm Trial Exhibit 7, '777 patent, col. 6, ll. 5-6. Based upon my experience, I do not believe that improvement of the potency or toxicity results of pioglitazone over the prior art were surprising in the context of medicinal chemistry.

42. In the '777 patent, the inventors disclosed on Table I that pioglitazone reduced blood glucose and triglycerides by a little over 3 times that found in the 3, 4, or 5 methyl compounds. That is hardly a substantial improvement whereby one would be surprised at the result, even for the very conservative change from methyl substituent to an ethyl substituent, as in pioglitazone, on the same basic compound. Persons of ordinary skill in the art would be motivated to make just such a conservative change precisely because they have a reasonable expectation of success of improving the lead compound in this way. A conservative change would be expected to maintain the very high potency of the 6 methyl, while "tweaking" it slightly to reduce its unwanted side effects, i.e., weight gain and brown fat increases.

43. Moreover, it is puzzling to me that Takeda chose not to bring to the examiner's attention the existence of the '779 patent. In that patent, Takeda had already claimed the novelty and utility of lower alkyls such as methyl and ethyl substituents on pyridyl rings. Alphapharm Trial Exhibit 5, col. 20, claims 1-6. Thus, Takeda can hardly allege surprise at the beneficial results of substituting an ethyl for methyl on the pyridyl as it claimed in the '777 patent. If the

examiner had had the '779 patent before him, he may have held Takeda to a standard for surprising results higher than a mere 3 fold increase between some of the methyl-substituted pyridyls and the ethyl-substituted pioglitazone.

45. I state under penalty of perjury that the above is true and correct to the best of my personal knowledge.

Executed on: November 18, 2005

Henry I. Mosberg

SA122

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc., Plaintiffs, v. Ranbaxy Laboratories, Ltd., et al., Mylan Laboratories, Inc., et al., Watson Pharmaceuticals, Inc, et al., Alphapharm Pty, Ltd., et al., Defendants.	Civil Action No. 03 CV 8250 (DLC) 03 CV 8253 (DLC) 03 CV 8254 (DLC) 04 CV 1966 (DLC) (Consolidated for trial) Honorable Denise L. Cote

DECLARATION OF DOUGLAS R. MORTON, JR., PH.D.

SA123

TABLE OF CONTENTS

I. BACKGROUND 1

II. THE TAKEDA/UPJOHN COLLABORATION 4

III. DECISION TO DEVELOP PIOGLITAZONE (AD-4833) 12

IV. CONCLUSION 14

SA124

I. BACKGROUND

1. My name is Douglas Ross Morton, Jr., Ph.D.

2. I was born on August 5, 1945 in Chicago, Illinois. I currently reside at 5218 Grand Arbre Trail, Portage, MI 49024.

3. Currently, I am a member of the American Chemical Society, the American Diabetes Association, and the American Association for the Advancement of Science.

4. I received an A.B. (Chemistry Major, High Honors in Chemistry, magna cum laude) from Kenyon College, Gambier, Ohio in 1967.

5. I received my Ph.D. in Organic Chemistry from Columbia University, New York, NY (Research Advisor: Professor Nicholas J. Turro) in 1971.

6. I had a postdoctoral appointment in Organic Chemistry at Stanford University, Palo Alto, CA (Professor William S. Johnson - deceased) from 1971-1973.

7. I am the author of 45 peer-reviewed publications and a named inventor on 44 United States patents. Trial Exh. 102 is my curriculum vitae, which includes a complete list of my publications and patents.

8. I first joined The Upjohn Company as a Research Scientist in the Experimental Chemistry Research Department in Kalamazoo, MI in 1973. I worked in that capacity until 1981, during which time I invented and synthesized novel variants of naturally-occurring metabolites of arachidonic acid, a polyunsaturated fatty acid important to maintaining normal physiology, many with significant biological activity on blood platelets and on the gastrointestinal tract. I contributed to the structural elucidation of prostacyclin (PGI_2) and invented and synthesized novel, chemically stable analogs of this naturally-occurring substance for biological evaluation. I also selected compounds that were profiled for potential evaluation in humans for the treatment of platelet disorders.

9. From 1981 to 1984, I was the Research Head of Experimental Science I, at The Upjohn Company, in Kalamazoo, MI. In this position, I led a group of synthetic chemists in the discovery of novel variants of naturally-occurring metabolites of arachidonic acid. Through this position I assumed increasing responsibility for leadership of gastrointestinal ("GI") projects based on prostaglandin antisecretory and cytoprotection properties. I also led the initial drug development project team for arbaprostil (ARBACET), a gastric antisecretory and cytoprotective prostaglandin compound.

10. In 1984, and continuing through 1985, I assumed the position of Associate Director of Diabetes and Gastrointestinal Diseases Research, also at The Upjohn Company in Kalamazoo, MI. It was at this time that I assumed a leadership role for GI (chemistry and biology) and type 2 diabetes mellitus ("Type 2 Diabetes") (chemistry) drug discovery programs. I also ran the H^+-K^+ ATPase inhibitor drug discovery project, which led to a potential clinical candidate (PNU-69167; disaprazzole).

11. From 1985 to 1987, I was the Director of Diabetes and Gastrointestinal Diseases Research at The Upjohn Company. In this capacity, I assumed responsibility for drug discovery and development programs in GI and Diabetes. My research group prepared and evaluated compounds for the purpose of helping to decide whether they should be entered into The Upjohn Company's pharmaceutical development program. The compounds my group evaluated included pioglitazone (for the treatment of Type 2 Diabetes) and disaprazole (a depo-delivered H^+-K^+ ATPase inhibitor for peptic ulcer healing). I had the responsibility for managing collaborative interactions with various third-party firms for in- and out-licensed GI and Diabetes development candidates. These third-party firms included Chugai, Takeda, and Ono Pharmaceuticals.

12. I was the Director of Metabolic Diseases Research, at Upjohn from 1987 through 1990. In this position I assumed responsibility for Upjohn's drug discovery and development programs in Metabolic Diseases (diabetes and atherosclerosis). My research group prepared and/or evaluated compounds as development candidates for NIDDM (β-guanidinopropionic acid) and for atherosclerosis (fine particle COLESTID).

13. During the period from 1990 through 1991 I served as the Director of Medicinal Chemistry Research, at Upjohn.

14. In 1994 I was appointed as Vice President of Discovery Research, at Upjohn. My responsibilities expanded beyond Medicinal Chemistry to include all Discovery Chemistry functions (Computer-Assisted Drug Design, Protein Biochemistry, and Physical and Analytical Chemistry).

15. From 1995 through 2003 I served The Upjohn Company and its merged and successor entities, including: Pharmacia & Upjohn, Inc., Kalamazoo, MI; Pharmacia & Upjohn, Inc., Peapack, NJ; Pharmacia Corp., Peapack, NJ; and Pfizer, Inc., Peapack, NJ, in the following positions: Vice President of Discovery Research; Group Vice President of Technology Acquisitions and Operations, and Vice President of Worldwide Discovery and Strategic Alliances.

16. From November 2003 through the present I have been the Chief Executive Officer of the Southwest Michigan Innovation Center, located in Kalamazoo, MI. In this capacity, I am responsible for assisting the scientific advancement of tenant/client companies, insuring the Center's operational intactness, nurturing connections between the Center and the external community, and monitoring and evaluating bioscience trends on the regional, national and international levels.

17. From 2003-2004, I was a member of the Scientific Advisory Board of Celltech R&D Ltd., Slough, Berkshire, England. I was a member of the Board of Directors of TissueInformatics, Inc., Pittsburgh, PA, from 2003 until the company was acquired by Paradigm Genetics in March of 2004. I have been a member of the Industrial Advisory Board of Cleveland Clinic Foundation Innovations, Cleveland, Ohio since 2004. I am a member of the following Boards of Directors: Icoria, Inc. (formerly Paradigm Genetics, Inc.), Research Triangle Park, NC; Core Technology Alliance Corporation, Ann Arbor, MI; and MichBIO, Lansing, MI. I am presently also serving as interim CEO of Icoria, Inc., Research Triangle Park, NC.

18. I am in no way being compensated for my testimony, although I am receiving reimbursement for my travel and legal expenses in connection with my testimony in this case. I have no interest in the outcome of this litigation.

II. THE TAKEDA/UPJOHN COLLABORATION

19. When I assumed the Associate Directorship of the Diabetes and Gastrointestinal Research Unit at The Upjohn Company in 1984 I became involved in the Takeda/Upjohn collaboration in researching thiazolidinediones. While that was the beginning of my involvement, that collaboration had already been ongoing for some years. By 1984, Upjohn and Takeda had already investigated ciglitazone [Takeda internal no. ADD-3878, Upjohn internal no. U-63,287] among many other thiazolidinediones. Ciglitazone, the first thiazolidinedione that was regarded as a pharmaceutically viable option, was synthesized by Takeda in the late 1970s. Through the early 1980s, Takeda and Upjohn collaborated in the development and testing of ciglitazone. In fact, ciglitazone had made it through the initial stages of human clinical trials until such work was discontinued,

primarily because long-term administration was found to cause cataract formation in rats.

20. By 1983, ciglitazone had been dropped and numerous other thiazolidinediones had been tested. The data on these compounds showed that thiazolidinediones generally were capable of lowering blood glucose and plasma triglycerides in animals presenting symptoms of Type 2 Diabetes, and of lowering triglycerides in normal animals, but exhibited significant toxicities when administered in therapeutically effective doses. From these findings it was concluded that thiazolidinediones seemed somehow able to ameliorate "insulin resistance" (i.e., a condition in which the body no longer responds (in varying degrees) to insulin's message to metabolize glucose), and so were sometimes described as "insulin sensitizers."

21. Notably, Upjohn and Takeda's investment of time, resources and capital into this research went against the grain of then-current industry thinking. I recall that Upjohn faced frequent challenges on its approach from other leaders in the diabetes field for pursuing thiazolidinediones for the treatment of Type 2 Diabetes, instead of the then-industry standards - insulin secretagogues (i.e., compounds which attempted to combat insulin resistance by causing the pancreas to create more insulin) and treatment of late-stage sequelae (late-stage consequences of Type 2 Diabetes, such as neuropathy, nephropathy, and retinopathy). Throughout the mid 1980s, scientists from other major pharmaceutical companies made it known that they believed research into insulin sensitizers to be in an unestablished, unproven, and risky direction. Our understanding, at the time, was that diabetes researchers and management at these companies thought insulin sensitizers to be a form of radical and unfounded thinking in diabetes treatment.

The Takeda/Upjohn partnership was a pioneering collaboration in a new direction of diabetes treatment involving insulin sensitization. As a result, however, we were also working in largely uncharted terrain.

22. An example of the evolution in our knowledge and thinking can be found in an article entitled, Sohda T. et al., "Studies on Antidiabetic Agents II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives," Chem. Pharm. Bull. 30:3580-3600 (1982)) ("Sohda II") [Trial Exh. 076]. This reference teaches that Compounds 57, the unsubstituted 2-pyridyl {5-[4-[2-(2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione} and 58, the 6-methyl substituted 2-pyridyl {5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione} "caused considerable increases in body weight and brown fat weight." Id. at 3589 At the time, it was known that brown fat had to do with thermogenesis in rodents but we were not sure of a direct correlation with physiology in humans. We also knew that brown fat could have something to do with sugar metabolism, but were, again, unsure of any relationship to human physiology. These were then matters of scientific debate. We did, however, know that the pathology of Type 2 Diabetes, referred to at the time as Non-Insulin Dependent Diabetes Mellitus ("NIDDM"), suggested that obesity contributed to insulin resistance. We also knew that, generally speaking, obesity and any increase in obesity in a patient suffering from NIDDM was thought to be a clear adverse health effect. Therefore, because of data indicating that pyridyl derivatives caused such adverse health effects, people involved in or interested in this research, reading Sohda II at the time, myself included, would conclude that this reference taught away from the pyridyl compounds.

23. As research continued, however, we came to the conclusion that increases in body weight and brown fat weight were sometimes a corollary to effectiveness in thiazolidinediones, and that brown fat was not a significant factor in humans. However, based on the wealth of data available to us, it seemed clear that this class of compounds was characterized by common toxicities to the eye (cataracts), heart, liver and red blood cells (anemia). See Trial Exh. 081 (A-15-13, p. 17, TAK-00383425, 442). From the point of view of toxicity, these effects became more important than brown fat or body weight gain.

24. In developing a successor to ciglitazone, our primary focus was on finding a compound that did not exhibit these toxicities, and which was five to ten times more potent than ciglitazone.

25. Of particular concern to our team was cataractogenesis. Cataract formation was an important toxicology parameter in the United States Food and Drug Administration (FDA). Based on this understanding and the fact that it was found to occur with ciglitazone, both Takeda and Upjohn placed a strong emphasis on the test used to indicate cataractogenesis, which was known as the chick lens assay. See Trial Exh. 107 (Upjohn Letter Regarding Utility and Importance of in vitro Chick Lens Assay, TAK-00384319-20); Trial Exh. 108 (Letter from Upjohn to Takeda Discussing Chick Lens Screen, TAK-00384321); Trial Exh. 082 (Minutes of March 13, 1984 Strategic Meeting, TAK-00366984-86). A failure in the in vitro chick lens assay would cause a compound to be ruled out for development.

26. Similarly, cardiomegaly (increase in heart weight) was of paramount concern. Were a compound to exhibit statistically significant heart enlargement, it too would be precluded from further consideration.

27. Thus, by 1984 Takeda and Upjohn had a wealth of data resulting from years of research, but lacked a promising successor compound which exhibited sufficient pharmacological activity without the toxicity that ended ciglitazone's development. Because of this extensive work, Takeda and Upjohn researchers were among the most skilled in the field. This group of scientific investigators had certainly reviewed, if not authored, likely all of the publicly available information regarding thiazolidinediones. Despite this wealth of information and expertise, however, researchers involved in the Takeda/Upjohn collaborstion were without a clear path by which to develop a thiazolidinedione compound that would be both effective and safe.

28. During the early-to-mid 1980s, there was no way that anyone could reliably predict the degree of efficacy or toxicity of various structural thiazolidinedione derivatives. They had to undergo time and resource-intensive testing in animals. Even a seemingly simple change in chemical structure can have a profound impact on the biological activity of a molecule, because a relatively minor structural change may change various aspects of the molecule including its shape or overall conformation, electron density, and/or its physical properties (e.g., solubility), all of which affect the way in which a molecule may interact with its protein target(s) (sometimes referred to as receptors). This was further complicated by the fact that, at the time, the particular receptor at issue (and so its relevant binding pocket) were unknown. One simply could not predict the impact of such a change on the protein-binding that the molecule is interacting with that might be responsible for its biological effects.

29. As a result, Takeda and Upjohn used a "shotgun" approach to thiazolidinedione development, yielding data on a vast number of compounds. That data was then analyzed

to see if we could discern a relationship between chemical structure and biological properties. Some comparisons were relevant and some were not. Of the compounds not blacked out in Table 1 of the A-15-34 report (described later) (Trial Exh. 083), I would consider a comparison of pioglitazone to ciglitazone to be the starting point, given the amount known about the latter compound. I would then want to compare pioglitazone to the other alkyl substituted pyridines. I would not consider a comparison between pioglitazone, a 5-ethyl pyridyl [alkyl-substituted] compound, and ADD-3894, an unsubstituted compound, to be as immediately critical as the comparisons to alkyl-substituted pyridines because the structural and electronic properties of an alkyl-substituted pyridine ring differ from those properties in an unsubstituted-pyridyl compound.

30. Given all these considerations, Upjohn and Takeda used this "shotgun" approach to development in searching for a post-ciglitazone compound, both to increase efficacy and to get away from its toxicity. This approach was discussed at and memorialized in the Minutes of Takeda-Upjohn Meeting on Collaboration in Antidiabetic Drug Discovery, dated March 13, 1984. Trial Exh. 082 (TAK-003669S4-86). I was at that meeting and have an independent recollection of it. To the best of my recollection, these minutes accurately reflect the happenings of that meeting.

31. As memorialized in the meeting minutes, Takeda was to "select about 50 antidiabetic leads on the basis of hypoglycemic activity in the KKAy mouse and the Wistar-fatty rat. Aside from potency, the selection criteria should also include uniqueness in chemical structure." Id. (TAK-003669S4-86). Such "uniqueness in chemical structure," was part of our plan for finding a safe alternative to ciglitazone. We were concerned that toxicity

problems might be general to thiazolidinediones and/or to particular sub-structures within some of the molecules. Thus, "structural uniqueness" adds information from a structure activity point of view, and lessens the likelihood of finding that compounds with similar structure exhibit similar toxicities. Another structural consideration revolves around the scalability of a compound, concerning whether the compound could be synthesized on a commercial scale. Of note, I cannot recall any mention or concern of patentability at any meeting between Takeda and Upjohn during the period from March of 1984 through January of 1986. The mission of our collaboration was focused on identifying a compound that was efficacious and of extremely low toxicity.

32. Generally, of course, patentability is eventually a consideration for all research-based drug companies, because that exclusivity is the only way that they can recuperate the enormous investment needed to discover and develop new drugs. But in our thiazolidinedione research and selection process patentability was not a driving consideration.

33. In the agreements reached at the meeting of March 13, 1984, responsibilities were divided between and among Upjohn and Takeda and a timetable set. As the minutes reflect, the fifty compounds originally identified were to be narrowed to about ten, then five, then one. We agreed to a further meeting in August of 1984 to jointly review our research and to select nine to ten leads, to be further narrowed to four to five leads. Unfortunately, the work proved difficult, and some delays set back the schedule by roughly three months, so the meeting set for August 1984 took place at the end of October, 1984.

34. Before the October 1984 meeting, Upjohn carried out its own testing of many if not all of the 50-odd compounds selected for investigation by Takeda. Some of the compounds selected for evaluation had already undergone analysis in the Upjohn laboratories prior to March of 1984, such as ADD-3878 (ciglitazone) and ADD-3959. See Trial Exh. 106 (TAK-00384340-41); Trial Exh. 107 (TAK-00384319-20); Trial Exh. 108 (TAK-00384321). I cannot now recall the particulars of the many compounds that we analyzed, but I clearly recall that we independently assayed some if not all of the fifty "leads" selected by Takeda.

35. I know that Upjohn carried out various efficacy and toxicity experiments on these "lead" thiazolidinedione compounds, including the in vitro chick lens assay and four-day efficacy screens in KKA^y (diabetic) mice.

36. In the early 1980s (I cannot recall a specific date) Takeda had provided Upjohn with a breeding colony of KKA^y mice specifically for use in testing potential antidiabetic compounds for efficacy. See Chang AY et al., "The Upjohn Colony of KKA^y Mice: A Model for Obese Type II Diabetes," in Diabetes, at 466-470 (1985) (Trial Exh. 110). During the collaboration, these animals were used in the screening and evaluation of thiazolidinedione chemotypes related to the collaboration.

37. Although I do not recall the exact KKA^y experimental protocol used at Upjohn, I have seen the A-15-34 report which was discussed at the October 1984 meeting, and Upjohn's test protocol was substantially similar, if not identical to, the protocol described in that document. Trial Exh. 083 at TAK-00400122 (A-15-34).

38. I was of the belief in the early-to-mid 1980s and am today that the KKA^y mouse represents the best disease model to identify and develop antidiabetic compounds relative

to humans. The blood profiles of KKA^{y} mice are very similar to humans and therefore provide a very accurate in vivo model of Type 2 Diabetes in humans.

39. KKA^{y} mice are, however, very sensitive animals. Changes in light, noise and temperature in addition to other external stimuli can affect mating, reproduction, litter sizes and mortality, and pharmacological responses. Investigators using this model had to keep these sensitivities in mind when evaluating data from this model. Investigators had to determine whether a given experimental result was due to a pharmacological response. Importantly, investigators must have a feel for the compounds' respective properties to know whether an experiment was meaningful or flawed. In consideration of an investigator's knowledge and evaluation it was acceptable, and in many cases necessary, to disregard an experiment which, based on this knowledge and experience, was flawed and therefore produced unreliable data.

III. DECISION TO DEVELOP PIOGLITAZONE (AD-4833)

40. In late October, 1984, I traveled to Osaka, Japan with Drs. Dulin and Lund of The Upjohn Company to meet with senior Takeda scientists and management to select a new compound for codevelopment.

41. At this meeting a Takeda scientist (whom I cannot remember) presented a summary report containing Tables 1 and 2 found in the A-15-34 report (Trial Exh. 081). Although I do not recall reviewing the A-15-34 report in its entirety, I do have an independent recollection of Tables 1 and 2 and the data contained therein. The data on these tables formed the basis for our joint decision to focus on five particular compounds (marked in handwritten circles on Table 2) and to pursue development of pioglitazone. We relied on this summary data as the basis for our decision to develop pioglitazone. These summary

reports were the fruit of many months of labor and consisted of the synthesis of thousands of pages of data, data from both sides of the Pacific.

42. Upjohn did not have a policy of attempting to recreate or verify each and every one of Takeda's experimental results as communicated in these types of documents. Upjohn received data regarding hundreds of compounds. Verifying each and every endpoint for each and every compound would have been an imprudent use of our combined, yet limited resources. Notably, however, Upjohn did not rely solely on Takeda's efficacy and toxicity data when making its development decisions. Although there was a free exchange of data, in its own business interest Upjohn performed its own independent analyses on compounds that appeared interesting for further study (including many of the A-15-34 compounds). Through this testing, Upjohn, without exception, confirmed the data that Takeda summarized in its reports that were forwarded to Upjohn. Furthermore, the relationship with Takeda was such that Upjohn could have access to any compound it chose for confirmatory testing. Trial Exh. 103 (Takeda/Upjohn Co-development Agreement, TAK 00097692-95). In the history of my involvement with the pioglitazone project, there was never any disagreement between data reported to Upjohn by Takeda and the data that Upjohn independently generated (within typical variation inherent in animal experimentation) or the conclusions drawn from that data.

43. AD-4833 (pioglitazone) was a joint selection at the October 30, 1984 meeting. There was some discussion between Upjohn and Takeda on the issue of potency versus safety (therapeutic ratio). Trial Exh. 084 (Takeda Notes, TAK-00366387-92)[1]; Trial Exh. 086

[1] I have an independent recollection of a discussion of this subject matter at the October 30, 1984 meeting in Osaka. Although I do not recall seeing these notes at the time, this document accurately reflects Takeda's initial presentation of data at our meeting on October 30, 1984.

(Minutes of Upjohn/Takeda Meeting of October 30, 1984, TAK-00384248-50)[2]. The key parameter to Upjohn was the therapeutic ratio (safety ratio)[3] of a candidate compound - Upjohn selected pioglitazone on this basis. Takeda preferred some of the far more potent compounds, although they had greater toxicity and thus a narrower therapeutic index. In the end, the decision made by Upjohn and Takeda was collaborative and in total agreement: pioglitazone met our criteria of being five to ten times more potent than ciglitazone, it exhibited extremely low toxicity ("clean" at 100mg/kg/day and in the chick lens assay), and was superior in terms of its therapeutic index to all other compounds investigated. Pioglitazone was the only compound that was "clean" in all toxicity parameters of concern, namely, the in vitro chick lens assay, heart, liver, and erythrocytes.

44. We continued through 1984 to evaluate each of the five compounds selected at the October 1984 meeting. Based on interim data from longer-term (90 day) toxicological analysis of the five lead compounds, pioglitazone was the only compound that proved to be clean. On March 7, 1986, Takeda and Upjohn reached a final consensus that AD-4833 (pioglitazone) would be the candidate for development. See Trial Exh. 087 (Meeting Minutes of March 7, 1986, TAK-00384557-58).

IV. CONCLUSION

45. Over the course of my many dealings with Takeda, I found Takeda and its researchers to be solid scientists, and an extremely honest and ethical business partner. Upjohn and Takeda had a wonderful collaborative relationship, a relationship founded on mutual trust

[2] I have an independent recollection of reviewing these minutes and of the topics of discussion at the meeting. These minutes accurately reflect that subject matter.
[3] The wider the margin between the minimum efficacy and the minimum toxicity of a compound the greater the therapeutic ratio, or safety margin, of that compound.

SA138

and confidence arising from the quality of the scientific work. Personally, I hold Takeda's scientists, particularly Drs. Meguro, Fujita, Sobda, Ikeda, and Iwatsuka in the highest regard. I have worked extensively with these scientists and have, on many occasions, reviewed Upjohn data that confirmed their methods, data, assessments, evaluations, and conclusions.

I declare under penalty of perjury that the foregoing is true and correct. Executed on November 16, 2005

Douglas Ross Morton, Ph.D.